FRAILTY, CARDIOVASCULAR FUNCTION AND RISK OF FALLING AMONGST PATIENTS WITH STAGE 5 CHRONIC KIDNEY DISEASE ON HAEMODIALYSIS

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Abstract

This PhD thesis explores the risk of falling of stage 5 chronic kidney disease (CKD-5) patients receiving haemodialysis (HD) therapy. Previous research has suggested that multiple risk factors such as older age, comorbidities, polypharmacy, and frailty contribute primarily to the increased risk of falling in this clinical population. However, HD patients are also characterised by severe cardiovascular disease burden that often manifests with symptoms of orthostatic intolerance, impaired blood pressure control and syncope, all of which may be implicated in the aetiology of falling. The aim of this thesis was to address important research questions, such as: Are frailty and its physical function/activity components associated with falling in CKD-5 patients on HD? Are baroreflex function and the cardiovascular responses to orthostasis also associated with falling? What is the relative importance of frailty and cardiovascular function as potential exercise-modifiable risk factors for falls in this patient group?

A prospective observational study involving 76 prevalent HD patients (61.1±14 years) confirmed previous observations that CKD-5 patients on HD are at higher risk of falls compared to the non-uraemic population, as 37.7% of research participants experienced at least one fall during a 12-month follow-up, and the incidence of falls recorded was 1.16 falls/person-year. Although participants classified as fallers did not appear to differ from non-fallers in single physical function measures such as timed-up and go (TUG), 5 repetitions chair sit to stands (CSTS-5), or muscle strength, frailty and lower postural balance were associated with increased odds of falling. In addition, baroreflex function indices reflecting frequency of baroreflex activation, as well as the blood pressure response to a five-minute 60° head-up tilt test (HUT-60°) were associated with increased odds of falling and a greater number of falls. More importantly, we showed that modelling the risk of falling by adding a cardiovascular function variable to a frailty-only model improved significantly the prediction of number of falls experienced by CKD-5 patients on HD.

Overall, this PhD thesis revealed that cardiovascular mechanisms implicated in the short-term regulation of blood pressure showed a greater relative importance than frailty in predicting falls in the study participants. These findings challenge the current assumption that frailty is the primary factor involved in the aetiology of falls in CKD-5 patients on HD. The clinical implications of this novel observation are also discussed from a preventive and rehabilitative perspective.

Key words: Stage 5 chronic kidney disease, haemodialysis, falls, frailty, cardiovascular function.

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Abbreviations

AbsVel	Absolute velocity
ADL	Activities of daily living
AIC	Akaike's information criterion
AP	Anterior-posterior
APD	Automated peritoneal dialysis
Area95	95% confidence ellipse area
AUC	Area under the curve
BEI	Baroreceptor effectiveness index
BMI	Body mass index
BP	Blood pressure
BPV	Blood pressure variability
BRS	Baroreflex sensitivity
CAPD	Continuous ambulatory peritoneal dialysis
CCI	Charlson comorbidity index
CKD	Chronic kidney disease
CKD-5	Stage 5 chronic kidney disease
Cl	Chloride
CO	Cardiac output
ContBP	Continuous blood pressure
ContDBP	Continuous diastolic blood pressure
ContmBP	Continuous mean blood pressure
ContSBP	Continuous systolic blood pressure
COP	Centre of pressure
CRP	C-reactive protein
CSTS-5	5 repetitions chair sit to stand
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DMMS	Dialysis Mortality and Morbidity Study

DOPPS	Dialysis Outcomes and Practice Pattern Study
EC	Eyes closed
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
EO	Eyes open
ESRD	End stage renal disease
FES	Falls efficacy scale
GFR	Glomerular filtration rate
GROS	General register office for Scotland
Hb	Haemoglobin
HD	Haemodialysis
HDL	High-density lipoprotein
HF	High frequency
HR	Hazard ratio
HR	Heart rate
HRV	Heart rate variability
HUT	Head up tilt
HUT-60°	HUT at 60°
ICG	Impedance cardiography
IPAQ	International physical activity questionnaire
IPAQ	International physical activity questionnaire
K	Potassium
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	Low-density lipoprotein
LF	Low frequency
MAP	Mean arterial pressure
MCS	Mental component summary score
ML	Medial-lateral
MVC	Maximal voluntary contraction
Na	Sodium

NHS	National Health System
NN	Normal to normal
OR	Odds ratio
OscBP	Oscillometric blood pressure
PA	Habitual physical activity
PCS	Physical component summary score
PIS	Participant information sheet
POMA	Performance-oriented mobility assessment
PTH	Parathyroid hormone
RangeX	Range of COP displacement along the ML axis
RangeY	Range of COP displacement along the AP axis
REC	Research ethics committee
RMSX	Root mean square displacement along the ML axis
RMSY	Root mean square displacement along the AP axis
ROC	Receiver operating characteristics
RR	Rate ratio
RRI	R-R interval
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SDNN	Standard deviation of normal to normal intervals
SERPR	Scottish Electronic Renal Patient Record
SF-36	Short form health survey
SP	Sway path
SPPB	Short physical performance battery
SRRR	Scottish renal registry report
SV	Stroke volume
TPR	Total peripheral resistance
TUG	Timed up and go
UKRR	UK renal registry
UN	United Nations

URR	Urea reduction ratio
USRDS	US renal data system
VelX	Velocity along the ML axis
VelY	Velocity along the AP axis
WHO	World Health Organization

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CHAPTER 1: GENERAL INTRODUCTION AND LITERATURE REVIEW

1.1 GENERAL INTRODUCTION TO CKD-5

1.1.1 Stage 5 chronic kidney disease

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of chronic kidney disease (CKD) defines kidney disease as an abnormality of the kidney structure or function with repercussions on health, which can occur abruptly and may either resolve or become chronic (KDIGO CKD work group., 2013). CKD is a term that represents a variety of disorders affecting the kidney structure and function for > 3 months with variable clinical manifestation. The diagnosis of CKD is based on the presence of markers of kidney damage, such as albuminuria, altered albumin-to-creatinine ratio, electrolyte abnormalities deriving from tubular disorders, urine sediment abnormalities, or other histologic or structural abnormalities detected by imaging, and/or decreased glomerular filtration rate (GFR) (Levin et al., 2014). Overall, it is recommended to classify CKD in terms of cause and GFR and albuminuria categories. Nevertheless, the severity of CKD is most commonly classified based on different thresholds of GFR, and a classification in 5 stages of organ impairment, presented below, is currently used by nephrologists worldwide:

Table 1.1. Classification of CKD based on severity of kidney impairment.

CKD stage	GFR (ml/min/1.73m^2)	Kidney function
CKD-1	> 90	Normal or high
CKD-2	60 – 89	Mildly decreased (relatively to young adults levels)
CKD-3a	45 – 59	Mildly to moderately decreased
CKD-3b	30 – 44	Moderately to severely decreased
CKD-4	15 – 29	Severely decreased
CKD-5	< 15	Kidney failure

Stage 5 CKD (CKD-5) is the last, and more severe, stage of CKD and is also sometimes referred to as end-stage renal disease (ESRD). The main feature of CKD-5 is the kidney failure which requires renal replacement therapy (RRT) to guarantee survival (National Kidney foundation 2002).

RRT can take the form of peritoneal dialysis, haemodialysis (HD), or kidney transplantation (Schena et al., 2000), out of which HD therapy is the most common option for incident patients (UK Renal Registry (UKRR) 2016). HD is a treatment that consists of an extracorporeal removal of the waste products, such as urea and creatinine, which cannot be eliminated otherwise by the non-functioning kidneys. This treatment is usually performed in an outpatient dialysis centre, or at home in some cases, thrice weekly for 3 to 5 hours depending on the patient's size.

1.1.2 Prevalence and incidence of CKD-5

About 6% of the UK population is estimated to be affected by stages 3 to 5 CKD (Roderick et al., 2011). In 2010, over 2,500,000 people were estimated to be undergoing RRT worldwide, and the large majority, around 78%, were receiving dialysis either in the form of peritoneal dialysis or HD, while the remainder were living with a renal transplant (Liyanage et al., 2015). In the UK, this equates to 61,256 people suffering from CKD-5 requiring RRT in 2015 (UKRR 2016), a substantial increase of 39% compared to the 2006 UKRR projections (UKRR 2006). This increase in incidence over a period of 10 years may reflect the worrying rapid increase of this health condition and subsequent high costs for the National Health System (NHS), which is the main provider for health care and treatment in the UK for almost all CKD-5 patients. Hospital HD is the most common form of dialysis in the UK, with 41% of RRT patients requiring this treatment modality (UKRR 2016), and it is also the most expensive, with a yearly estimated cost per patient of over £ 35,000 (Baboolal et al., 2008).

In 2015, 5026 people were receiving RRT in Scotland, according to the Scottish Renal Registry Report (SRRR) and 42% of them were treated with dialysis (SRRR 2016). Among these dialysis patients, 86% were undergoing hospital-based HD, 2.5% were

performing home HD, while 3% and 8% were using continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) respectively. The health burden arising from CKD-5 and therefore from RRT has been increasing at an alarming rate in Scotland, considering that the annual incidence of RRT has almost tripled from 37 to 106 per million population in the last 30 years (SRRR 2016).

Similar trends emerge from the U.S., where in 2015 the annual incidence of ESRD was 378 per million population, which has also almost tripled in the last 30 years (USRDS 2017). In addition, the most common treatment for ESRD in the U.S. is HD, as the large majority (63%) of patients requiring RRT is maintained with this treatment (USRDS 2017).

The most common cause of CKD-5 in the UK remains diabetes, which accounts for 27.5% of the single primary renal diagnoses (UKRR 2016), and is followed by glomerulonephritis (14.1%), polycystic kidney (7.4%) and hypertension (6.8%). These trends are also reflected in Scotland, where diabetes is the lead cause of CKD-5, with 28% of all primary renal diagnoses (SRRR 2016). Interestingly, the last 50 years have seen a reshaping of the leading causes of CKD-5 due to the rampant increase of type 2 diabetes mellitus (Winocour 2018): in the 1960-1971 decade, 40% and 0% of the patients starting RRT were diagnosed with glomerulonephritis and diabetic nephropathy respectively, as the cause of renal failure. More than 40 years later, these figures were reversed with 16% and 28% of incident RRT patients diagnosed with glomerulonephritis and diabetes as primary renal diagnosis (SRRR 2016).

Lastly, the median age of CKD-5 patients requiring RRT has also increased in the last 10 years. Particularly, the median age of prevalent patients requiring RRT has increased by 4 years since 2005, with HD patients being significantly older (median= 67 years) than patients maintained on peritoneal dialysis (median= 64 years), and patients living with a kidney transplant (median= 54 years) (UKRR 2016).

1.1.3. Prognosis and survival in CKD-5

The 2012 KDIGO guidelines recommend considering the following information when predicting prognosis of CKD: 1) GFR category, 2) albuminuria category, 3) the cause of CKD, 4) comorbidity levels and other risk factors (Levin et al., 2014).

Table 1.2. Prognosis of CKD based on GFR and albuminuria categories.

			Albuminuria categories (description and range)		
			Normal to mildly increased	Moderately increased	Severely increased
			< 30mg/g	30 – 300mg/g	> 30mg/g
GFR categories (ml/min per 1.73 m2)	CKD-1	> 90			
	CKD-2	60 – 89			
	CKD-3a	45 – 59			
	CKD-3b	30 – 44			
	CKD-4	15 – 29			
	CKD-5	< 15			

Green: low risk (no CKD in absence of other markers of KD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

The same model (Table 1.2) is also recommended to make the decision as to when to refer a patient to the specialist services for a timely planning of RRT (Table 1.3), before the patient reaches the CKD-5 stage. A timely referral to the specialist is defined as a time ≥ 1 year (Levin et al., 2014).

Table 1.3. Recommendations for a timely referral to the specialist services for planning RRT.

			Albuminuria categories (description and range)		
			Normal to mildly increased	Moderately increased	Severely increased
			< 30mg/g	30 – 300mg/g	> 30mg/g
GFR categories (ml/min per 1.73 m2)	CKD-1	> 90		Monitor	Refer*
	CKD-2	60 – 89		Monitor	Refer*
	CKD-3a	45 – 59	Monitor	Monitor	Refer
	CKD-3b	30 – 44	Monitor	Monitor	Refer
	CKD-4	15 – 29	Refer*	Refer*	Refer
	CKD-5	< 15	Refer	Refer	Refer

*Referring clinicians may want to discuss about the local arrangements for referral with their nephrology service.

In North America and in the UK, the most common modality of RRT for incident patients is HD therapy (USRDS 2017; UKRR 2016): after 90 days upon starting RRT, 67.3% of CKD-5 patients were maintained on HD in the UK.

Although HD is a life-saving treatment in CKD-5, the prognosis of these patients remains very poor as dialysis initiation is associated with a decline in functional status, low health-related quality of life and frailty (Johansen et al., 2013). In addition, survival analyses show that the relative one-year risk of death for prevalent RRT patients aged 35-39 is roughly 22 times higher than the non-uraemic population (UKRR 2016). The 1-year survival rate, 90 days after starting RRT, was even lower in Scotland compared to the UK average (83.1% vs 90.2%) in 2015 (SRRR 2016), and the 5-year survival rate was as low as 43% for those started on RRT between 1996 and 2011. Considering patients of all ages, the 10-year survival drops to 25%.

In 2015, the most common causes of death in CKD-5 patients undergoing RRT were due to cardiovascular disease (22%), followed by infection-related deaths (21%) and RRT withdrawal (14%) (UKRR 2016).

1.1.4 Impact of CKD-5 on general health and current management

While the very early stages of CKD are often asymptomatic, progression to CKD-5 frequently leads to clinical manifestation of symptoms such as tiredness, nausea, and itchiness arising from the impaired ability of kidneys to regulate fluid and electrolyte balance and eliminate metabolic by-products. Further complications are hypertension, bone and mineral disease, and anaemia (Murabito et al., 2018) as a result of the compromised capacity of kidneys to produce erythropoietin, which is required to produce red blood cells. In addition, CKD represents a model of premature and accelerated ageing, mainly as a result of chronic inflammation, activation of pro-ageing mechanisms, sympathetic-vagal imbalance and alteration of the stress resistance pathways (Kooman et al., 2014). The main features of this premature ageing are muscle wasting, and consequent physical function deterioration, but also accelerated vascular ageing (London 2018). Moreover, vascular disease can also affect the small vessels in the brain which could lead to white matter lesions (Bronas et al., 2017), and therefore a so-called "triad" of physical, vascular and cognitive impairment often results from this state of premature ageing. The sum of these symptoms and complications translate into a high burden of disease that is typically manifested through increased cardiovascular risk, high number of hospitalisations and overall lower quality of life (Balogun et al., 2017).

In the context of CKD-5, the clinical health management consists of RRT primarily, in the form of dialysis or kidney transplantation, followed by pharmacological treatment to correct high blood pressure and blood and bone deficiencies, and nutritional interventions to carefully adjust the diet (Romagnani et al., 2017). In addition to these current prevailing management plans, the Kidney Disease Outcomes and Quality Initiative (KDOQI) and the KDIGO clinical practice guidelines for the management of CKD (Inker et al., 2014; KDIGO CKD work group., 2013) have encouraged nephrologists to promote physical activity in CKD patients to counteract the progressive decline in physical function.

However, this practice remains largely inconsistent among renal healthcare providers (Zelle et al., 2017) and is an area that necessitates further guidance to improve the health management of these patients. Particularly, CKD-5 patients maintained on HD are in great need of physical activity counselling to counteract the well-known detrimental effect of dialysis-related sedentary behaviour on physical function (Manfredini et al., 2012), which may accelerate the onset of frailty. The high frailty rates observed in CKD-5 (Kojima et al., 2017), in conjunction with ageing processes (UKRR, 2016) are also responsible for adverse health outcomes that are typically managed by the geriatric medicine, such as falls and fall-related injuries.

1.2 LITERATURE REVIEW

1.2.1 General introduction to falls in the general population

1.2.1.1 Estimates of falls in the non-uraemic population

The World Health Organization (WHO) global report on falls prevention in older age (WHO 2008) states that approximately 28%-35% of people aged 65 years and older experience at least one fall every year. This proportion increases even more with older age and higher frailty levels, as 32%-42% of people older than 70 years of age are thought to fall each year, and up to 50% of elderly residents of nursing homes may experience falls at least once a year (WHO 2008).

These data are alarming in light of the fact that the global population is ageing. By 2050, the number of people aged 60 years and older would have more than doubled, and particularly the segment of the population that is expanding more rapidly is the over 80 years old group, which is predicted to constitute 20% of the older population by 2050 (UN 2004). Although survival into older age can be regarded as evidence of success of medical and pharmaceutical advancements, the growing number of older adults is most likely to result into an increase of falls-related injuries and relative medical expenses.

Falls can result in a variety of injuries, need for medical attention interventions, hospitalisations and even death. It is estimated that the rates of emergency department visits due to falls-related injuries, in Australia and in the UK, amount to 550-890 per

million population, and the falls injury rates resulting in hospital admission range from 160-300 per million population in the segment of the population aged 60 years and older (WHO 2008). The most common injuries that lead to hospitalisations, as a consequence of a fall, encompass traumatic brain injuries, upper limb injuries, and hip fracture. In the population over 65 years of age, these and other falls-related injuries account for more than 50% of the hospital admission due to injury (WHO 2008). In particular, hip fractures seem to have the most tragic consequences among all the falls-related injuries, as they require longer hospitalisation periods and approximately one in five patients dies within 1 year after sustaining a hip fracture as a result of a fall (Zuckerman 1996).

Overall, falls represent two thirds of deaths from unintentional injuries in older adults, which is the fifth cause of death in this sub-section of the population, after cardiovascular disease, cancer, stroke and pulmonary diseases (Rubenstein et al., 2006).

1.2.1.2 The economic burden of falls

Falls and fall-related injuries have a considerable economic impact on the health systems that is going to increase even further due to current predictions and upward trends in average and older age groups in the global population.

The WHO global report on the prevention of falls in older age (2008) characterised the economic burden of falls in terms of direct and indirect costs. The direct costs reflect expenses by the health care systems for medications and services for the treatment and rehabilitation of injuries arising from falls. The greatest of these expenses is the cost for hospital inpatient services (WHO 2008). The cost of hospitalisations for falls-related injuries depends greatly on the country of interest and, generally speaking, these projections are available for the developed countries only.

NHS data (2008) suggest that, due to the global aging population, the number of fallers over 85 years of age could increase from 100,000 to 200,000 over the next 20 years, with an estimated increase in direct costs from falls of £200 million. In addition to these costs, the WHO also highlighted some indirect costs for the household economy which are attributable to the possible productivity loss of family caregivers (WHO 2008).

1.2.1.3 Risk factors

The WHO global report on the prevention of falls in older age (2008) has identified several risk factors that are linked to an increased risk of falling. These risk factors can be grouped in four main categories, namely biological, behavioural, environmental, and socioeconomic factors. Falls often result as a complex interaction of these.

Biological risk factors refer to the physiological state of the human body and encompass both non-modifiable factors such as gender and age, and partly modifiable factors like the physical decline and the comorbidity burden and symptoms associated with ageing. A great number of prospective cohort studies and systematic reviews have concluded that muscle weakness, unsteady gait, poor balance, cognitive and visual impairments are the main biological risk factors for falls in the population of community-dwelling older adults (Tinetti et al., 1988; Rubenstein et al., 2006; Ambrose et al., 2013; Enderlin et al., 2015; Cuevas-Trisan et al., 2019). In addition, it has been pointed out that these biological factors often interplay with environmental and/or behavioural factors in the aetiology of falling (Klenk et al., 2017). For instance, some behavioural factors such as lack of physical exercise/sedentary behaviour will contribute to the loss of muscle mass, which is an inevitable consequence of the ageing process, while engaging in an active lifestyle and following exercise programs aimed to maintain endurance, strength, flexibility have been shown to prevent falls by reducing the risk of developing chronic diseases (Cuevas-Trisan 2017). In addition to the lack of exercise, other behavioural risk factors of falls include the use/misuse of multiple medications/substances or an excessive alcohol intake, and the use of inappropriate footwear (WHO 2008). All these risky behaviours are highly modifiable and should therefore be considered in multifaceted interventions for the prevention of falls.

Along with the behavioural factors, the environmental risk factors are also modifiable. This category of risk refers to the interaction between the physical conditions of one individual and the potential environment hazards, both at home and in public spaces. It should be acknowledged that this class of factors does not constitute a risk of falling per se, but rather it's the combined effect of underlying personal risk factors and the exposure to the environmental ones that can result in falls and falls-related injuries. Established

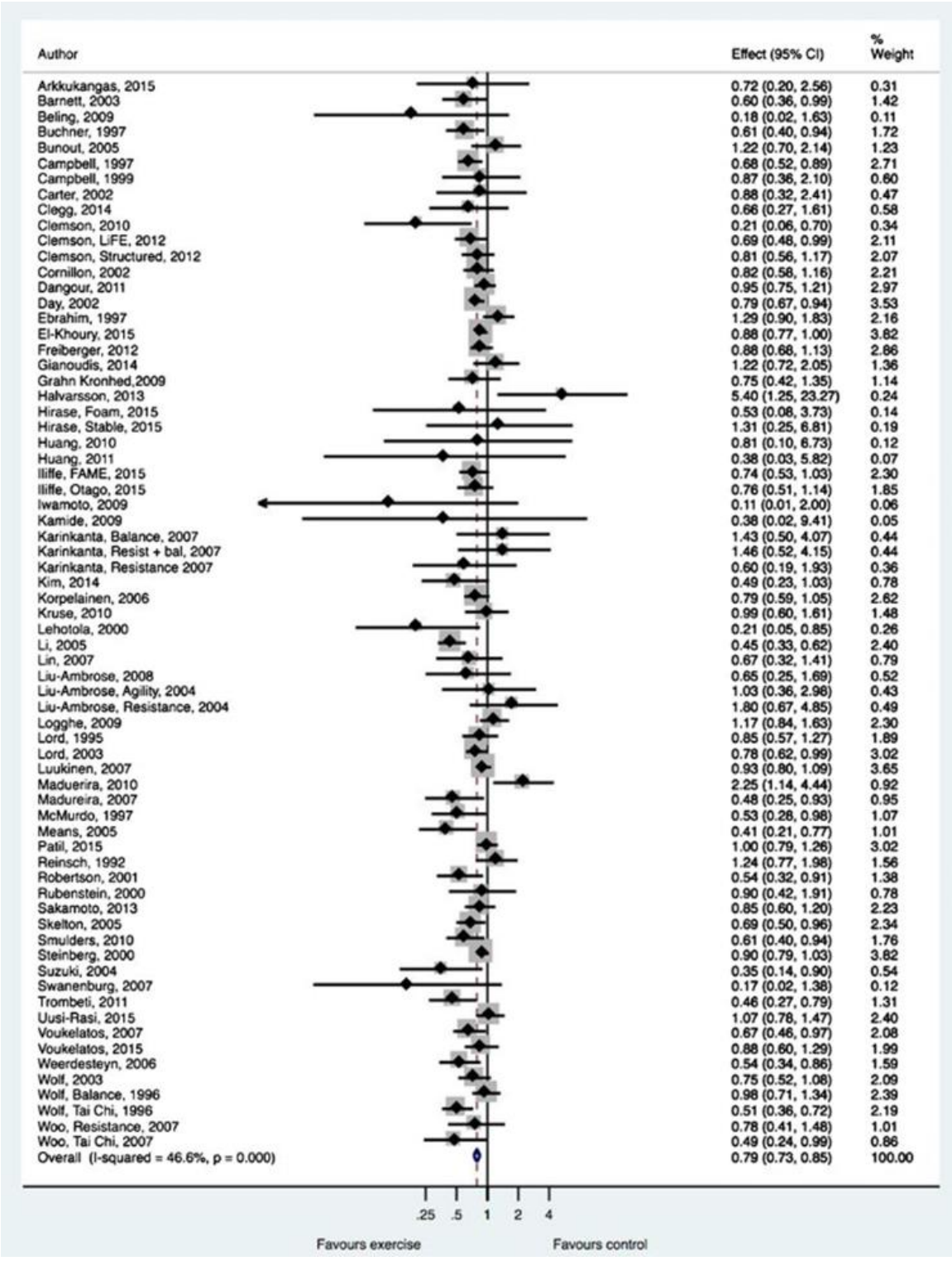
environmental risk factors for falls are: poor building design, poor lightening in public places or at home, cracked or uneven sidewalks, and slippery surfaces and stairs (WHO 2008).

Lastly, the WHO identified a further category of risk factors, namely the socioeconomic factors, which reflect how the economic status and the social conditions of individuals may influence the risk of falling. These risk factors encompass low income and education levels, lack of social interaction, inadequate housing, lack of community resources, and limited access to health and social services.

Even though various elements of the four categories cited above may be modified by different kind of interventions aimed to decrease the risk of falling, the WHO highlighted that two categories in particular are highly responsive to focused and evidence-based interventions, namely the environmental and behavioural risk factors. It is estimated that 30% to 50% of falls are attributable to environmental causes (Rubenstein et al., 2006), therefore home and public-modification of the environment play an important role in the prevention of falls in the elderly population.

Behavioural change is the other key element to address in order to minimise risk of falling. Generally speaking, this can be achieved by adopting an active lifestyle and by limiting risky behaviours like alcohol and substance misuse. Physical exercise has been the main interest of much research in efforts to prevent falls (Figure 1.1). A Cochrane systematic review highlighted how single exercise modalities were the most common intervention in randomised trials aimed to reduce falls in older adults living in the community (Gillespie et al., 2012). This review concluded that home and group-based exercise interventions reduced both the risk of falling and the rate of falls in this population. In addition, another Cochrane systematic review recently concluded that the most effective exercise interventions to reduce falls in elderly people are the ones involving balance and functional exercises primarily (Sherrington et al., 2019). These authors concluded that a combination of balance and resistance training is also probably effective in preventing falls.

Figure 1.1. Forest plot of exercise trials to reduce falls in older adults living in the community. Exercise versus control (Sherrington et al., 2017, p. 1752).



1.2.2 Falls in the population of CKD-5 patients on HD

1.2.2.1 Premise

Several prospective cohort studies conducted in CKD-5 populations have highlighted that 26.3% to 55% of HD patients suffer at least one fall every year (Abdel-Rahman et al., 2011; Polinder-Bos et al., 2014). The incidence of falls in these patients ranges from 0.38 to 1.76 falls/patient-year (Abdel-Rahman et al., 2011; Roberts et al., 2007). These estimates of falls are elevated compared to those of non-uraemic individuals and a recent systematic review concluded that dialysis patients are a group of people at high risk of falling (Lopez-Soto et al., 2015). These findings are of clinical importance because HD patients are at high risk of fractures (Dey et al., 2017), and an accidental fall may worsen quality of life and the burden of disease in these patients, who tend to have low functional status and high frailty rates already.

This PhD thesis will contribute to expand the currently available epidemiological data on falls in the CKD-5 population of patients maintained on HD, and will also explore which factors are most likely to contribute to falls in this group of people. In particular, this PhD research project will focus on the identification of which exercise-modifiable factors may be more closely associated with an increased risk of falling in HD patients. Findings arising from this thesis will inform researchers and healthcare providers about prioritization of outcome assessment for monitoring, and hopefully managing, falls risk in the CKD-5 population on HD.

1.2.2.2 Estimates of falls

The first study that investigated the risk of falls in HD patients was published by a British research group in 2003 (Roberts et al., 2003). The investigators reported observations from clinical practice that a greater number of HD patients were being referred to the specialist falls services, possibly due to the increased proportion of older (>65 years) CKD-5 patients starting RRT. Therefore, they hypothesised that a combination of risk factors encompassing old age, CKD-5-related autonomic failure, and hypotensive spells, triggered by HD therapy and/or by antihypertensive medications, could lead to orthostatic hypotension and to an increased number of falls in these patients. Although this first study

was limited in sample size (n° of study participants= 47) and in the methodology of falls appraisal (not-otherwise specified recall of falls in the previous year), the investigators concluded that HD patients have a high incidence of falls, with 27.7% of patients recalling at least one fall in the past year, as well as significant post-dialysis postural hypotension and occurrence of hypotensive symptoms.

Similarly to Roberts et al., (2003), a Canadian research group also reported their findings on the prevalence of falls among HD patients over 65 years of age (Cook et al., 2005). The rationale for their investigation was also based on the observation that the dialysis population was older on average, as 50% of CKD-5 patients starting RRT were aged 65 years and older in Canada at the time of the study (Canadian Institute for Health Information, 2002). The authors hypothesised that this age shift in patients starting RRT could potentially lead to a substantial increase of adverse outcomes, such as falls and falls-related morbidity, which are typical problems managed by geriatric medicine services. Particularly, patients over 65 years treated with dialysis would have the well-established risk factors of falling for senior citizens, namely muscle weakness, unsteady gait, poor balance, etc. (Rubenstein et al., 2006), as well as additional complications, such as the fluid and electrolyte shifts, that result from HD therapy and that may expose them to an additional risk of dizziness, hypotension and falls compared to the non-uraemic population. The results on the prevalence of falls among the patients from the two dialysis centres involved in this study were remarkably similar to those of Roberts and colleagues, as 27% of these patients reported at least one fall in the previous 12 months. The authors concluded that falls are highly prevalent in older HD patients, and also that the true prevalence of falls might have been underestimated in their investigation due to the retrospective observational method of falls ascertainment, which could result in recall inaccuracies (Cummings et al., 1988).

The first study that investigated the incidence of falls in HD patients prospectively was conducted by Desmet et al., (2005). This study aimed to highlight the possible risk factors of falls as well as to describe the incidence of falls among HD patients from seven HD units in Belgium. Although the ascertainment of falls was obtained over a relatively short follow-up period (8 weeks), the results from the study indicated that the estimated

incidence of falls in these patients was 1.18 falls/patient-year, approximately 2.4 times higher than the incidence previously described in non-institutionalised senior citizens (O'Loughlin et al., 1993). Therefore, the authors concluded that the risk of falling in CKD-5 patients on HD was higher than in the general healthy population of older adults.

A further prospective investigation on the incidence of falls and associated risk factors was conducted by Cook and colleagues in 2006 (Cook et al., 2006). This was the first study that extended the observational follow-up of falls to at least 12 months and consequently, it provided important information on the yearly incidence of falls in CKD-5 patients undergoing HD therapy. This research group also concluded that the risk of falling in HD patients was higher than in the non-uraemic population. Both the incidence of new fallers and number of falls were extraordinarily high, with 47% of patients experiencing at least one fall over the 12-month follow-up period (an excess of approximately 17% compared to healthy older adults (WHO 2008)), and 27.8% with two or more falls. The incidence of falls was even higher than the incidence estimated by Desmet et al., (2005), with 1.60 falls/persons-year.

After the first study published in 2003, Roberts et al., (2007) conducted a prospective observational study of the incidence of falls, syncope and dizziness in HD patients to corroborate the results emerged from their preliminary study. In addition to a high incidence of falls of 1.76 falls/persons-year in patients over 65 years of age, with 38% of them experiencing at least one fall over 6 months, this work also highlighted a frequent occurrence of dizziness, syncopal and pre-syncopal events in dialysis patients of all ages. Dizziness in particular was very common, as 78% of patients of all ages reported this symptom during the 6-month observational follow-up, while about 49% of patients reported they experienced a near-faint, which was classified as a pre-syncopal event, at least once.

Abdel-Rahman and colleagues (2011) conducted a prospective cohort study of the incidence of falls, over a 12-month follow-up period, and the long-term morbidity related to these falls in two HD centres in the US. Overall, 26.3% of the patients experienced one fall during the prospective observational period. However, those aged 65 years and older fell more frequently, as 38.2% reported at least a fall during the follow-up, compared to

the 16.7% of the patients younger than 65 years. The incidence of number of falls sustained was also higher in the older group of patients, with 0.59 falls/persons-year for the patients over 65 years of age as opposed to the 0.21 falls/persons-year of the younger group of patients.

Different results on the role of age were found by McAdams-DeMarco et al., (2013), who conducted a prospective cohort study aimed to explore the association between frailty and falls in CKD-5 patients undergoing HD therapy in a single dialysis centre in the U.S. In this study, 28.3% of the study participants reported at least one fall during a follow-up visit 6 months after the baseline assessment. No significant difference in terms of falling behaviour was found between younger and older HD patients, as 25.9% and 29.3% of patients younger and older than 65 years respectively experienced at least one fall over the follow-up period.

A remarkably similar prevalence of fallers among HD patients of all ages was found in a large cross-sectional study (Kutner et al., 2014). This study examined the association between potentially modifiable risk factors and history of falls in 762 prevalent HD patients in the U.S: 28.4% of these patients reported having fallen in the past 12 months, and 16.3% had multiple falls.

Polinder-Bos et al., (2014) found a much higher proportion of fallers among elderly dialysis patients from two HD centres in the Netherlands. The appraisal of falls was conducted prospectively, over 12 months, in this investigation: 55% of the study participants experienced at least one fall during the observational follow-up, and 41% of patients with falls were classified as recurrent fallers.

In a more recent study, Kono et al., (2018) conducted a prospective study over a longer observational follow-up period in Japan. This research group reported that 41% of their study participants fell at least once during the 2-year study period. Unfortunately, they did not report the number of falls experienced by patients, and therefore the incidence of falls cannot be calculated.

A very high incidence of falls was reported by Noto-Kadou-Kaza et al., (2015), who conducted a prospective investigation of falls in younger (mean age= 40.23 years) HD patients, over a short follow-up period (4 weeks). About 23% of patients fell at least one

time over this observational period, and the yearly incidence of the number of falls was estimated to be 3.2 falls/persons-year.

The lowest proportion of patients experiencing at least one fall over 12 months was found by Wang et al., (2017), who conducted a prospective longitudinal study to examine the relationship between physical functioning measures and falls in a group of HD patients. They found that only 16% of these patients had experienced falls over one year period: it should be acknowledged though that, even if the study was conducted prospectively, the ascertainment of falls was obtained exclusively at the end of the 12-month observational follow-up period, by means of a self-administered questionnaire. Therefore, the information on falls is likely to be subjected to a higher recall bias compared to those prospective studies which used more frequent (bi-weekly/monthly) follow-ups during the observational period.

In addition to the studies cited above, two investigations examined the incidence of falls that were severe enough to require presentation to an emergency department (Rossier et al., 2012), or hospitalisation (Delgado et al., 2015). These studies were conducted prospectively over a longer follow-up period and found comparable results: Rossier and colleagues reported that 28.6% of their study participants had experienced at least one severe fall over a mean follow-up of 20.6 months, while Delgado reported 283 first events for fall and/or fracture in 1053 HD patients, resulting in 26.9% of patients experiencing a severe fracture over a median follow-up of 30 months.

Lastly, a Canadian research group addressed the research question as to whether CKD-5 patients maintained on peritoneal dialysis had a similar incidence of falls of patients undergoing HD therapy (Farragher et al., 2014). They conducted a prospective cohort study of the incidence of falls and associated risk factors in 74 peritoneal dialysis patients over a period of 15 months: the results highlighted that 54% of these patients experienced at least one fall during the follow-up, and also that the incidence of falls was very high with 1.7 falls/persons-year. Therefore, the authors concluded that the risk of falling in these patients is higher than in the general population, and the results also suggest that, regardless of their treatment modality (e.g. peritoneal dialysis/HD), the risk of experiencing falls is high in all CKD-5 patients on dialysis.

1.2.2.3 Study designs and methodological considerations

The study designs and methods of the studies investigating the risk of falling in HD patients are synthesised in Table 1.4. The large majority of these studies used an observational prospective design to capture the falls-related information (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; Abdel-Rahman et al., 2011; Rossier et al., 2012; McAdams-DeMarco et al., 2013; Farragher et al., 2014; Polinder-Bos et al., 2014; Noto-Kadou-Kaza et al., 2015; Delgado et al., 2015; Wang et al., 2017; Kono et al., 2018), while only three studies used a cross-sectional design with retrospective data relating to falls (Roberts et al., 2003; Cook et al., 2005; Kutner et al., 2014).

The research setting in which the studies were conducted varied from one (Roberts et al., 2003) to 14 (Kutner et al., 2014) dialysis centres in the UK, Canada, Belgium, U.S., Switzerland, Netherlands, Morocco, Australia, and Japan. One study abstracted data from a subgroup of patients from the Comprehensive Dialysis Study, a large prospective cohort study conducted in 297 Renal Units across the U.S. (Delgado et al., 2015). Due to the great heterogeneity in the research settings, the sample sizes of the different studies also differed considerably. The smallest number of patients studied was 47 (Roberts et al., 2003), while the largest was 1053 (Delgado et al., 2015). Nevertheless, an even larger study was conducted by Naylor et al., (2014) who investigated the incidence of fracture in CKD by means of a population-based cohort study in 679114 patients diagnosed with CKD.

In all those studies with retrospective designs, the history of falls information relates to the previous 12 months (Roberts et al. 2003; Cook et al., 2005; Kutner et al., 2014), while the observational follow-up of the falls-related information in the prospective studies ranged from 4 weeks to 36 months (Naylor et al., 2014; Wang et al., 2017).

Another crucial methodological aspect is the operational definition of a “fall”. While a few studies did not provide a clear definition of a “fall” (Roberts et al., 2003; Roberts et al., 2007; McAdams-DeMarco et al., 2013; Noto-Kadou-Kaza et al., 2015), the most common definition adopted was “an event that resulted in a person coming to rest inadvertently on the ground or other lower level" (Desmet et al., 2005; Cook et al., 2006; Abdel-Rahman et al., 2011; Rossier et al., 2012; Kutner et al., 2014; Farragher et al., 2014;

Polinder-Bos et al., 2014; Kono et al., 2018). Other similar definitions were less exhaustive, such as “a fall to the ground or lower level” (Cook et al., 2005), or more detailed, such as “an incident in which the body unintentionally comes to rest on the ground or other lower level which is not as a result of a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure" (Wang et al., 2017). Other studies restricted the operational definition of a fall to only those falling events that were severe enough to require presentation to an emergency department, hospitalisations, or fractures (Rossier et al., 2012; Delgado et al., 2015; Naylor et al., 2014).

The observational method used to collect the falls-related data plays also a determinant role on the heterogeneity of the study results on the incidence of falls, along with the follow-up duration. All retrospective studies did not differ in terms of observational method used, as the prevalence of falls was simply obtained by asking the participants if they had experienced any falls in the previous 12 months (Roberts et al., 2003; Cook et al., 2005; Kutner et al., 2014). The studies with prospective designs, on the contrary, were more heterogeneous with regard to the modalities of falls ascertainment. The most common observational method for these studies was an interview on the occurrence of any possible fall by a research nurse, on a weekly basis (Desmet et al., 2005; Polinder-Bos et al., 2014; Noto-Kadou-Kaza et al., 2015), or every couple of weeks (Cook et al., 2006; Farragher et al., 2014). The most frequent ascertainment of falls was used by Roberts et al., (2007), who administered a questionnaire on falls to the study participants during each HD session for 6 months. The most infrequent ascertainments, on the other hand, were performed by McAdams-DeMarco et al., (2013) and Wang et al., (2017), who obtained self-reported information about falls from the study participants only at the end of the observational follow-up period. Only in one study, the interviews on the occurrence of falls were carried out by a nephrologist (Abdel-Rahman et al., 2011). As for those studies that investigated the incidence of severe falls only, the information relating to these falls was abstracted from the patients’ medical records or from other electronic documentation that was generated automatically as a result of the admission to an emergency department/hospitalisation (Rossier et al., 2012; Naylor et al., 2014; Delgado et al., 2015).

Table 1.4. Summary of studies investigating risk of falling in patients on dialysis. Study designs and methodological considerations.

Author	Population	Study design	Sample size	Observational period	Definition of a fall	Observational method
Roberts et al., 2003	CKD-5 patients on HD.	Retrospective cross-sectional study.	47.	Previous 12 months.	Not provided.	Patients were asked if they had fallen in the previous 12 months.
Cook et al., 2005	CKD-5 patients on HD.	Retrospective cross-sectional study.	135.	Previous 12 months.	Not provided.	Patients were asked if they had fallen in the previous 12 months.
Desmet et al., 2005	CKD-5 patients on HD.	Prospective observational study.	308.	8 weeks.	"An event that results in coming inadvertently to the ground".	HD nurses interviewed patients on the occurrence of falls for an 8-week period, at least one a week.
Cook et al., 2006	CKD-5 patients on HD.	Prospective cohort study.	162.	Median: 468 days (365-506 range).	"An event that resulted in a person's coming to rest inadvertently on the ground or other lower level".	Biweekly patient interviews in the HD centre by a research nurse.
Roberts et al., 2007	CKD-5 patients on HD.	Prospective cohort study.	78.	6 months.	Not provided.	HD nurses administered a falls questionnaire during each dialysis treatment session for a 6-month period.

(Continued)

Table 1.4. *(Continued)*

Author	Population	Study design	Sample size	Observational period	Definition of a fall	Observational method
Abdel-Rahman et al., 2011	CKD-5 patients on HD.	Prospective cohort study.	76.	12 months.	"An event which resulted in a person coming to rest inadvertently on the ground or other lower level".	Weekly interviews by a nephrologist in the HD centre.
Rossier et al., 2012	CKD-5 patients on HD.	Prospective cohort study.	84.	Mean: 20.6 months.	"A fall requiring presentation to an emergency department, and/or hospitalisation".	Severe falls were recorded based on the visits to the emergency departments of the study hospital, or other affiliated hospitals.
McAdams-DeMarco et al., 2013	CKD-5 patients on HD.	Prospective cohort study.	95.	Median: 6.7 months.	Not provided.	Patients who survived at least 5 months self-reported the number of falls at the follow-up visit.
Kutner et al., 2014	CKD-5 patients on HD.	Retrospective cross-sectional study.	762.	Previous 12 months.	"An event that resulted in a person coming to rest inadvertently on the ground, floor or other lower level".	Patients self-reported falls occurred during the previous 12 months.

(Continued)

Table 1.4. *(Continued)*

Author	Population	Study design	Sample size	Observational period	Definition of a fall	Observational method
Farragher et al., 2014	CKD-5 patients on chronic peritoneal dialysis.	Prospective cohort study.	74.	15 months.	"An event that resulted in a person coming to rest inadvertently on the ground or other lower level".	Patients (and/or caregivers) were contacted by telephone, or face to face, every 15 days.
Polinder-Bos et al., 2014	CKD-5 patients on HD and chronic peritoneal dialysis.	Prospective observational study.	49.	12 months.	"An event which resulted in a person coming to rest on the ground or another lower level".	HD nurses interviewed patients on a weekly basis during the first three months, and phone calls once a month after the third month.
Naylor et al., 2014	All stages CKD patients.	Prospective cohort study.	679114.	3 years.	Not provided.	Six databases were used to extract information on falls with hospitalisation, and fractures.
Noto-Kadou-Kaza et al., 2015	CKD-5 patients on HD.	Prospective observational study.	70.	4 weeks.	Not provided.	Patients were interviewed weekly on the occurrence of falls for 4 consecutive weeks.

(Continued)

Table 1.4. *(Continued)*

Author	Population	Study design	Sample size	Observational period	Definition of a fall	Observational method
Delgado et al., 2015	CKD-5 patients on HD.	Prospective cohort study.	1053.	Median: 2.5 years (25th - 75th percentile= 1.0 - 3.9 years).	Falls or fractures that were severe enough to require medical evaluation via Medicare claims data or hospitalisation.	Falls and fractures were identified through Medicare claims data.
Wang et al., 2017	CKD-5 patients on HD.	Prospective exploratory longitudinal study.	51.	12 and 36 months (primary and secondary end-point).	"An incident in which the body unintentionally comes to rest on the ground or other lower level which is not as a result of a violent blow, loss of consciousness, paralysis, or an epileptic seizure".	The patients completed a falls questionnaire (at 12 and 36 months) asking about falls occurred in the preceding 12 months.
Kono et al., 2018	CKD-5 patients on HD.	Prospective observational study.	223.	24 months.	"An event that resulted in a person's body part, coming into contact inadvertently with the ground or floor".	Nursing staff ascertained whether the study participants fell or not at each dialysis treatment.

1.2.2.4 Demographics

The demographic characteristics of study participants from the studies investigating the risk of falling in HD patients are summarised in Table 1.5. The mean age of study participants was higher than 60 years old in most of the studies (Roberts et al., 2003; Cook et al., 2005; Desmet et al., 2005; Cook et al., 2006; Abdel-Rahman et al., 2011; Rossier et al. 2012; McAdams-DeMarco et al., 2013; Farragher et al., 2014; Polinder-Bos et al., 2014; Delgado et al., 2015; Wang et al., 2017; Kono et al., 2018), and a few of these studies included only patients over 65 years of age (Roberts et al., 2003; Cook et al., 2005; Cook et al., 2006; Farragher et al., 2014; Polinder-Bos et al., 2014). The mean age of the youngest study population was 40.3±16.8 years (Noto-Kadou-Kaza et al., 2015).

The shortest dialysis vintage of the study participants was 4.2 months (interquartile range: 3.7-4.9) (Delgado et al., 2015), while the longest was 162±81.6 months (Noto-Kadou-Kaza et al., 2015). Almost all studies included prevalent CKD-5 patients maintained on dialysis with a median dialysis vintage of 21.6 months (Rossier et al., 2012) or higher. Only one study included incident dialysis patients (Delgado et al., 2015).

Patient comorbidities were not described in three studies (Roberts et al., 2003; Cook et al., 2005; Roberts et al., 2007) and were generally reported as either the prevalence of comorbid conditions in the study population (Desmet et al., 2005; Abdel-Rahman et al., 2011; Rossier et al., 2012; Farragher et al., 2014; Polinder-Bos et al., 2014; Delgado et al., 2015; Kono et al., 2018) or the number of comorbidities (Cook et al., 2006; McAdams-DeMarco et al., 2013; Wang et al., 2017). Not surprisingly, the most common comorbidities found in the study populations were cardiovascular disease, with prevalence rates ranging from 22% (Kono et al., 2018) to 65% (Polinder-Bos et al., 2014), and diabetes, with prevalence rates ranging from 32% (Farragher et al., 2014) to 58.5% (Delgado et al., 2015). Other commonly reported medical conditions were depression, which was diagnosed in 8% (Polinder-Bos et al., 2014) to 23.8% (Rossier et al., 2012) of patients, and dementia, which was diagnosed in 1.9% (Desmet et al., 2005) to 11.9% (Rossier et al., 2012) of patients.

1.2.2.5 Characteristics of falls

Some prospective studies reported the characteristics of falls recorded over the follow-up period in terms of location, timing, and kind of activity leading to the fall.

All the studies that recorded information on the location of falls reported the patients' home as the most common site. Desmet et al., (2005) found that 82% of the falls occurred at home, 7% in public sites, and 9% in other locations, while Polinder-Bos et al., (2014) also confirmed that the most common location of falls was at home (57.5% of falls), followed by outdoors (35% of falls), the HD centre (5% of falls), and nursing homes (2.5% of falls). In addition, Rossier et al., (2012) highlighted that 54.2% of the falls were severe enough to require presentation to an emergency department occurred at home, 16.2% in the HD centre, 12.9% in a public site, and 12.9% during a hospitalisation. Noto-Kadou-Kaza et al., (2015) reported that 87.5% of falls occurred outside the HD centre.

As far as the timing of falls is concerned, some research has suggested that the post-dialysis period might be a critical time for falls (Roberts et al., 2003). This hypothesis does not seem to be confirmed by prospective studies, which did not find a clear relationship between the post-HD timeframe and the occurrence of falls (Cook et al., 2006; Abdel-Rahman et al., 2011; Rossier et al., 2012; Polinder-Bos et al., 2014). Only two prospective studies with a short follow-up reported that the majority of falls occurred after dialysis. Desmet et al., (2005) found that 61.5% of the falls happened within the 22 hours post-HD, while 23% of the falls recorded occurred within the 22 hours preceding HD therapy. Similarly, Noto-Kadou-Kaza et al., (2015) reported that 87.5% of the falls occurred after the dialysis session, nevertheless the definition of the post-dialysis period was not provided in the study. Conversely, Cook et al., (2006) observed that falls occurred on dialysis and non-dialysis days with a similar frequency, while two other studies found that only 30.8% and 50% (41% post-dialysis) of the falls occurred on a dialysis day (Abdel-Rahman et al., 2011; Polinder-Bos et al., 2014). Likewise, Rossier et al., (2012) highlighted that 37.5% of patients with falls experienced them within 24 hours after the last dialysis session.

Two studies also extracted information as to what kind of activity was associated with the falling event, and they both reported walking indoors as the most common activity

preceding a fall (Cook et al., 2006; Farragher et al., 2014). Cook et al., (2006) found that falling while walking indoors was the most frequent occurrence (29.8%), followed by standing up from the seated position (23.6%), walking outdoors (13.4%) and standing up from a lying position (9.2%). Farragher et al., (2014), on the other hand, documented that 51% of falls occurred when walking indoors, while 12% and 11% of falls occurred when walking outdoors and sitting down from the standing position.

1.2.2.6 Risk factors of falling

The risk factors of falling emerging from the studies described above are summarised in Table 1.5. A variety of risk factors for falls were identified with older age (Desmet et al., 2005; Roberts et al., 2007; Rossier et al., 2012; Kutner et al., 2014; Farragher et al., 2014; Delgado et al., 2015; Kono et al., 2018), previous history of falls (Cook et al., 2006; Rossier et al., 2012; Farragher et al., 2014), polypharmacy (Desmet et al., 2005; McAdams-DeMarco et al., 2013), depression and/or antidepressant use (Desmet et al., 2005; Rossier et al., 2012; Kutner et al., 2014), comorbidity (Cook et al., 2006; Farragher et al., 2014), frailty (McAdams-DeMarco et al., 2013; Kutner et al., 2014; Noto-Kadou-Kaza et al., 2015; Delgado et al., 2015), and low blood pressure with or without symptomatology (Roberts et al., 2003; Cook et al., 2006; Polinder-Bos et al., 2014; Noto-Kadou-Kaza et al., 2015; Kono et al., 2018) being the most commonly reported.

Contrasting results emerged for the effect of sex. Two studies found male gender to be associated with falls (Cook et al., 2006; Farragher et al., 2014), while three other studies reported female gender to be associated with falling behaviour (Abdel-Rahman et al., 2011; McAdams-DeMarco et al., 2013; Delgado et al., 2015).

A couple of studies (Roberts et al., 2003; Cook et al., 2005) did not seek to identify risk factors as such, although they described the study population by comparing patients with and without falls in terms of potential discriminative factors. Cook et al., (2005), for instance, found no significant differences in age ($p=0.32$) and sex ($p=0.28$) between fallers and non-fallers, while Roberts et al., (2003) reported that orthostatic hypotension was manifested in 34.8% of patients before dialysis, and in 69.6% after dialysis ($p= 0.02$), and there was a significant higher number of patients who had falls in the post-dialysis

orthostatic hypotension group (p-value not reported). Therefore, the authors suggested that post-dialysis hypotension may be associated with falls and syncope in HD patients. Four years later, the authors from this last study conducted a prospective investigation of the incidence of dizziness, falls, and syncope (Roberts et al., 2007). The results of this study indicated that age was significantly associated with falls, as 38% of patients over 65 years of age experienced at least one fall compared to only 4% of the younger patients ($p< 0.001$). However, no relationship between pre- and post-dialysis blood pressure, or post-dialysis orthostatic blood pressure and falls (or other symptoms, i.e. dizziness and syncope) was reported.

Desmet et al., (2005) identified older age (OR: 1.057/y, 95% CI: 1.013 - 1.103, p=0.01), diabetes (OR: 2.747, 95% CI: 1.175 - 6.410, p=0.02), total number of prescribed drugs (OR: 1.190/drug, 95% CI: 1.040 - 1.362, p=0.011), antidepressant use (OR: 5.263, 95% CI: 2.262 - 12.195, p= 0.0001), and failing to walk 10 meters (OR: 2.057, 95% CI: 1.321 - 3.202, p=0.001) as independent predictors of falls in logistic regression analysis. In addition, other physical function performance tests (arising, balance with eyes closed, one-leg standing) were significantly worse in the patients who had falls in univariate analysis only, while no differences were found in lying and standing post-dialysis blood pressure between fallers and non-fallers. Moreover, the authors also validated the predictive logistic model derived from their study in another cohort of patients who were also assessed for the same risk factors at baseline and for falls by means of a 6-month follow-up: the model was significant (p= 0.0099) and classified correctly 81.3% of these patients. An odds regression model was used by Cook et al., (2006) who found that previous history of falls (OR: 2.33, 95% CI: 1.22 - 4.45, p= 0.01), male gender (OR: 1.98, 95% CI: 1.02 - 3.81, p= 0.04), Charlson comorbidity index score (OR: 1.24, 95% CI: 1.04 - 1.47, p=0.01), mean pre-dialysis systolic blood pressure (OR: 0.85, 95% CI: 0.72 - 1.00, p= 0.05) were predictive of falls. In contrast to Desmet et al., (2005), no statistically significant association between age and falls emerged from the analysis (OR: 1.57, 95% CI: 0.93 - 2.65, p= 0.09). Also, no significant differences in physical performance measures between fallers and non-fallers were identified in this study.

Abdel-Rahman et al., (2011), on the other hand, found that both female gender (OR: 4.64, 95% CI: 1.61 - 14.45, p= 0.006) and older age (OR: 3.10, 95% CI: 1.09 - 9.42, p= 0.038) were associated with increased odds of falling in univariate logistic regression analysis. All the remainder factors potentially linked to falls, such as biochemistry values, comorbidity and blood pressure did not show any significant association with falling status in this study.

Rossier et al., (2012) conducted a prospective investigation of the risk factors for severe falls, resulting in admission to an emergency ward. This research group highlighted that age (OR: 1.13, 95% CI: 1.03 - 1.3, p= 0.009), depression (OR: 7.6, 95% CI: 1.8 - 32.6, p=0.006), malnutrition (OR: 8.4, 95% CI: 1.7 - 42.4, p= 0.01), previous history of falls (OR: 4.9, 95% CI: 1.2 - 19.4, p= 0.02) were associated with severe falling accidents in univariate logistic regression analysis. In this investigation, participants also underwent the performance-oriented mobility assessment (POMA): although patients who experienced falls tended to have lower POMA scores compared to patients free from falls, the POMA score was not found to be an independent predictor of falls.

The first study to highlight an association between frailty and falls in HD patients was performed by McAdams-DeMarco et al., (2013). In this study, the authors reported that frailty, assessed by means of the Fried's frailty phenotype (Fried et al., 2001) was predictive of a 3.09-fold higher number of falls in Poisson regression analysis (95% CI: 1.38 - 6.90, p= 0.006), after adjustment for age, race, sex, comorbidity, number of prescribed medications, disability, education, and marital status. In addition, female gender (1.84, 95% CI: 1.06 - 3.19, p< 0.05) was also associated with a higher number of falls in this study.

Kutner et al., (2014) also found a significant association of frailty with history of falls in a larger cohort of HD patients. In this retrospective study, frail patients were more than twice as likely to have had falls in the previous year (OR: 2.39, 95% CI: 1.22 - 4.71, p= 0.01). In addition, the multivariable logistic regression analysis showed that the study participants with depression and/or using antidepressants were more likely to be fallers (OR: 1.83, 95% CI: 1.23 - 2.74, p= 0.003) than participants without depression and not using antidepressants. Age (OR: 1.02, 95% CI: 1.01 - 1.04, p= 0.01) was also associated

with falling status, while the odds of having falls were lower in association with a higher cognitive function score (OR: 0.99, 95% CI: 0.97 - 0.99, p= 0.01).

The cognitive status was not associated with falls in a study by Farragher et al., (2014), who prospectively investigated the incidence of falls in CKD-5 patients on peritoneal dialysis. In this study, a multivariable random effects Poisson regression analysis revealed that the patients' previous history of falls (RR: 2.37, 95% CI: 0.98 - 5.70, p= 0.05) was the only statistically significant factor associated with higher number of falls. Nevertheless, the study participants who had falls were also more likely to be men, older, to have a shorter dialysis vintage and higher comorbidity. The results did not highlight any relationship between blood pressure and falls.

On the contrary, Polinder-Bos et al., (2014) found that the pre-dialysis systolic blood pressure was lower in a group of dialysis patients with falls compared to those who were falls-free (130±19 mmHg vs 143±22 mmHg, p= 0.04). The Cox regression analysis performed in this study showed that the risk of experiencing a fall increased by 30% for every 5 mmHg of lower pre-dialysis blood pressure (HR: 1.30, 95% CI: 1.03 - 1.65, p= 0.03). A rise of 10 ρmol/l in parathyroid hormone also increased the risk of falling by 22% (HR: 1.22, 95% CI: 1.06 - 1.39, p= 0.004). No significant differences in physical function status and medications were found between fallers and non-fallers in the same study.

A significant association between low blood pressure and falls was also reported also by Noto-Kadou-Kaza et al., (2015). In this short-term prospective study, the authors performed a multivariate logistic regression analysis which revealed that intradialytic hypotension was significantly associated with falls (OR: 2, 95% CI: 1.8-2.2, p=0.006). Frailty (p= 0.047) was also associated with the falling status in univariate analysis.

In agreement with the results of McAdams-DeMarco et al., (2013), Kutner et al., (2014), and Noto-Kadou-Kaza et al., (2015), self-reported frailty was found to be associated with a higher risk of first fracture or fall (HR: 1.60, 95% CI: 1.16 - 2.20, p< 0.01) in a larger prospective study (Delgado et al., 2015). The Cox proportional hazards regression analysis performed in this investigation also revealed that female gender (HR: 1.70, 95% CI: 1.33 - 2.17, p< 0.0001), white race (HR: 1.36, 95% CI: 1.02 - 1.82, p< 0.01), and age/per 10 years (HR: 1.20, 95% CI: 1.10 - 1.33, p< 0.0001) were associated with falls and fractures.

Wang et al., (2017) conducted a prospective longitudinal study of physical function, quality of life and falls in HD patients. The authors analysed the association between physical function and falls by means of negative binomial regression analysis. This analysis revealed that lower ankle dorsiflexion strength and lower mobility, assessed through the short physical performance battery (SPPB), predicted a higher number of falls after 12 months in univariate analysis (RR: 0.62, $p= 0.02$ and RR: 0.71, $p< 0.01$). After 36 months, lower mobility predicted a higher number of falls in both univariate and multivariate analysis (RR: 0.75, $p< 0.01$ and RR: 0.72 $p= 0.02$).

Lastly, a recent study aimed to develop and validate a fall-risk assessment tool (Kono et al., 2018). The development of such a tool was based on those factors that were significantly and independently associated with a higher number of falls during the observational study period: older age (HR: 1.67, 95% CI: 1.04–2.67), C-reactive protein (HR: 2.07, 95% CI: 1.10–3.90), low geriatric nutritional risk index (HR 1.04, 95% CI 1.01–1.08), low mobility, a score < 8 in the SPPB (HR 2.54, 95% CI 1.54–5.10), low handgrip strength (HR 1.57, 95% CI 1.04–2.36), and intradialytic hypotension (HR: 1.56, 95% CI 1.03–2.36).

1.2.2.7 Consequences of falls

The consequences of falls experienced by dialysis patients are summarised in Table 1.5.

The majority of the studies investigating falls in CKD-5 patients on dialysis reported the consequences and/or complications of the falls experienced by study participants. The most commonly reported complications of falls were fractures (Cook et al., 2005; Desmet et al., 2005; Cook et al., 2006; Rossier et al., 2012; Kutner et al., 2014; Farragher et al., 2014; Polinder-Bos et al., 2014; Naylor et al., 2014; Delgado et al., 2015), hospitalisations (Cook et al., 2006; Kutner et al., 2014; Farragher et al., 2014; Polinder-Bos et al., 2014; Bowling et al., 2018), and death (Cook et al., 2006; Rossier et al., 2012; Farragher et al., 2014; Li et al., 2008; Bowling et al., 2018).

Two retrospective studies reported that 4% (Cook et al., 2005) and 11.2% (Kutner et al., 2014) of the study participants who had reported falls in the previous 12 months experienced fractures as a result of these falls. Kutner and colleagues also reported that

71% of the patients who sustained these fractures, which mainly involved the hips, upper and lower limbs, were also hospitalised.

In the study by Desmet et al., (2005), 32% of the falls sustained by patients over the 8-week observational follow-up were complicated by fractures or wounds requiring medical care, while 10.7% of the falls recorded met the definition of a serious fall given by the authors, namely a fall requiring hospitalisation, or resulting in fracture or death.

Cook et al., (2006) found that 4% of the patients who had falls sustained fractures, 7% had head trauma with loss of consciousness, 16% required hospitalisation, and 4% died as a direct consequence of the fall-related injury within 7 days from the time of the fall. Overall, 19% of the falls required some form of medical attention.

The study conducted by Abdel-Rahman et al., (2011) revealed that 15.4% of the older group (over 65 years) and 14.3% of the younger group of HD patients suffered a severe injury (definition of severe injury not provided) as a direct consequence of the falls occurred during the prospective observational follow-up.

Rossier et al., (2012) conducted a prospective investigation of the incidence of falls that were severe enough to require presentation to an emergency room. The results from this study indicated that 54.8% of these falls were complicated by fractures: 35.3% of these fractures involved the hip, 17.7% the pelvis, and 11.8% the ribs. 3.2% of the falls also resulted in death as a consequence of the injuries sustained.

One study exploring the risk of falling in peritoneal dialysis patients (Farragher et al., 2014) reported that 6% of the falls incurred by these patients led to a fracture, 6% caused a head injury, 14% resulted in hospitalisation, and 24% required presentation to an emergency department. In addition, the authors conducted survival analyses over an extended follow-up period and found that the number of falls were a significant predictor of mortality (HR: 1.62, 95% CI: 1.29 – 2.02, $p< 0.001$).

In 2008, Li et al., (2008) also performed survival analyses on the results from a previous study investigating the incidence of falls in HD patients (Cook et al., 2006). Similarly to Farragher et al., (2014), the Cox regression analysis revealed that falls were an independent risk of death (HR: 1.78, 95% CI: 1.07–2.98, $p= 0.03$).

Polinder-Bos et al., (2014), and Noto-Kadou-Kaza et al., (2015) conducted two smaller prospective investigations of the incidence of falls in dialysis patients. The following complications of falls were described as part of their results: not otherwise specified minor complications in 53% of falls, fractures in 15% of falls, hospitalisation required in 15% of falls (Polinder-Bos et al., 2014); and haematoma in 41.18% of the patients who had falls, not otherwise specified wounds in 23.53%, dislocations in 5.88% (Noto-Kadou-Kaza et al., 2015). In addition, both authors reported that, overall, 45% of falls recorded (Polinder-Bos et al., 2014), and 47.05% of the patients with falls (Noto-Kadou-Kaza et al., 2015) required some form of medical help.

In the study by Naylor et al., (2014), the complications of falls as such could not be described as fractures only represented the primary outcome of this prospective investigation. Nevertheless, the authors reported the location of first fracture during follow-up for CKD-5 patients (hips: 54.2%, forearm: 19.2%, pelvis: 18.2%, proximal humerus: 8.4%).

More recently, Bowling et al., (2018) conducted a prospective investigation of the adverse health outcomes of severe falls-related injuries occurred in the year preceding HD initiation in older dialysis patients. The Cox regression analysis performed in this study revealed that patients with a positive history of severe fall injuries were at a significant higher risk of further serious fall-related injuries (HR: 2.65, 95% CI: 2.41–2.91), post-acute skilled nursing facility utilisation (HR: 1.40, 95% CI: 1.30–1.50), hospitalisation (HR: 1.11, 95% CI: 1.06–1.16), and death (HR: 1.14, 95% CI: 1.06–1.22).

Table 1.5. Summary of studies investigating risk of falling in patients on dialysis. Study findings.

Author	Prevalence of falls	Incidence of falls	Age	Sex	Risk factors	Consequences
Roberts et al., 2003	27.7%	Not available.	Mean: 78.2±5.3 years.	51%F 49%M	***Post-dialysis orthostatic hypotension*** was more frequent among those patients who had falls**.**	Not available.
Cook et al., 2005	27%	Not available.	Mean: 74.9±6.2 years.	61%M 39%F	No significant differences in age and sex were found between fallers and non-fallers.	4% of patients volunteered they had sustained a fracture or head injury as a result of the falls experienced.
Desmet et al., 2005	12.7%	1.18 falls/person-year.	Median: 70.9 years (range: 25-93).	56%M 44%F	***Older age***, ***diabetes***, ***total number of prescribed drugs***, ***antidepressant use***, and ***failing to walk 10 meters*** were independent predictors of falls in logistic regression analysis.	32% of falls were complicated by wounds requiring medical care or fractures. 10.7% of falls met the authors' definition of a serious fall.
Cook et al., 2006	47%	1.60 falls/person-year.	Mean: 74.7±6.1 years.	57%M 43%F	***Previous history of falls***, ***male gender***, ***comorbidity***, ***pre-dialysis blood pressure*** were predictive of falls in proportional odds regression analysis.	19% of falls required medical attention; 7% of fallers sustained head injuries with loss of consciousness; 4% sustained fractures; 16% were hospitalised; 4% died.

(Continued)

Table 1.5. *(Continued)*

Author	Prevalence of falls	Incidence of falls	Age	Sex	Risk factors	Consequences
Roberts et al., 2007	38%	1.76 falls/person-year.	Mean: 58 years.	34.6%F 65.4%M	There was a significantly higher incidence of falls in the ***older patients***.	Not available.
Abdel-Rahman et al., 2011	26.3%	0.38 falls/person-year.	Mean: 62.4±16.1 years.	38.2% F 61.8% M	***Age >65 years*** and ***female gender*** were associated with falls in univariate logistic regression analysis.	15.4% of elderly fallers and 14.3% of younger fallers sustained severe injury as a result of a fall.
Rossier et al., 2012	28.6%	0.22 severe falls/person-year.	Median: 69.5 years (range 26-85).	33%F 67%M	***Older age***, ***depression***, ***malnutrition***, ***previous history of falls***, and ***POMA*** were associated with severe falls in univariate logistic regression analysis.	54.8% of falls were complicated by fractures of the hip (35.3%), pelvis (17.7%), ribs (11.8%), and death (3.2%).
McAdams-DeMarco et al., 2013	28.3%	Not available.	Mean: 60.5±12.6 years.	46.3% F 53.7% M	***Frailty*** predicted a higher number of falls in Poisson regression analysis. ***Female gender***, ***medication use/drug***, ***high school education or higher*** were also associated with falls.	Not available.

(Continued)

Table 1.5. *(Continued)*

Author	Prevalence of falls	Incidence of falls	Age	Sex	Risk factors	Consequences
Kutner et al., 2014	28.4%	0.88 falls/person-year.	Mean: 57.1±14.1 years.	59.2%M 40.8%F	***Frailty***, ***depression***, ***older age***, and ***lower cognitive function*** were associated with increased odds of falling in multivariable logistic regression analysis.	11.2% of fallers sustained fractures (primarily involving the upper and lower limbs). 71% of these patients were hospitalised.
Farragher et al., 2014	54%	1.7 falls/person-year.	Mean: 76.2±7.5 years.	55%M 45%F	***Previous history of falls*** was associated with higher number of falls in multivariable random effects Poisson regression analysis.	6% of falls resulted in a fracture, 6% resulted in head trauma (reported by patient), 24% resulted in an emergency room visit, 14% led to hospitalisation.
Polinder-Bos et al., 2014	55%	0.85 falls/person-year.	Median: 79.3 years (range: 70-89).	71% M 29% F	***Lower pre-dialysis systolic blood pressure*** and ***higher parathyroid hormone*** were predictive of falls in Cox regression analysis.	53% of falls had minor complications, 15% were complicated by fractures, 15% required hospitalisation; 45% required medical help.

(Continued)

Table 1.5. *(Continued)*

Author	Prevalence of falls	Incidence of falls	Age	Sex	Risk factors	Consequences
Naylor et al., 2014	Not available.	Not available.	Mean: 62 years.	42.8%F 57.2%M	***Lower eGFR*** was associated with a higher number of fractures or falls with hospitalisation.	Location of first fracture in follow-up: Hip: 54.2%, Forearm: 19.2%, Proximal humerus: 8.4%, Pelvis: 18.2% (Group <15ml/min per 1.73m² eGFR or on dialysis).
Noto-Kadou-Kaza et al., 2015	22.9%	3.2 falls/person-year.	Mean: 40.3±16.8 years.	50%F 50%M	***Hypotension***, ***frailty***, and ***sensory deficit*** were associated with increased odds of falling in univariate logistic regression analysis.	The falls resulted in haematoma (41.2%), wounds (23.5%), dislocations (5.9%), and no consequences (29.4%). 47.1% of patients informed a doctor about the fall they had.
Delgado et al., 2015	26.9% of patients experienced either a severe fall or a fracture.	Not available.	Median: 63 years (52-73).	45%F 55%M	***Self-reported frailty***, ***female gender***, ***older age***, ***white race*** were associated with a higher risk of first fall or fracture in Cox regression analysis.	Not available.

(Continued)

Table 1.5. *(Continued)*

Author	Prevalence of falls	Incidence of falls	Age	Sex	Risk factors	Consequences
Wang et al., 2017	16%	Not available.	Mean: 63±13.7 years.	63%M 37%F	***Lower muscle strength*** and ***lower mobility (SPPB)*** were predictors of falls in univariate negative binomial regression analysis.	Not available.
Kono et al., 2018	41%	Not available.	Mean: 69.4±11.6 years.	60%M 40%F	***Older age***, ***C-reactive protein***, ***lower geriatric nutritional risk index***, ***SPPB***, ***low handgrip strength***, and ***intradialytic hypotension*** were associated with falls in Cox regression analysis.	Not available.

1.2.3 Frailty in CKD-5

Frailty is a biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes (Fried et al., 2001).

This syndrome was first defined by Fried et al., (2001), who studied the association between a phenotype of frailty and adverse outcomes such as falls, disabilities in activities of daily living (ADL), hospitalisations, and mortality in a large cohort of older adults from the Cardiovascular Health Study. The results from this study showed that this frailty phenotype was independently predictive of these adverse outcomes, and demonstrated for the first time that frailty is a construct at least partly independent from disability and comorbidity. Because of this qualitative distinction, the assessment of frailty in a clinical setting has gained attention in light of its preventability and potential reversibility, which would delay or hinder the onset of adverse health outcomes. The frailty phenotype introduced by Fried is characterised by five components: shrinkage, low levels of physical activity, poor strength, low gait speed and self-reported exhaustion. Those individuals who meet at least 3 out of the 5 criteria are defined as frail.

Although this is the most commonly used definition of frailty, other tools for the assessment of frailty have been developed since the Fried's phenotype was introduced. These tools encompass the Groningen frailty indicator (Steverink et al., 2001), the Clinical frailty scale (Rockwood et al., 2005), the Frailty Index (Rockwood et al., 2007), and the FRAIL scale (Morley et al., 2012), which represent either a modification of the Fried's frailty phenotype, or a quantitative assessment of increased vulnerability. For instance, the Frailty Index shifts the focus of attention to the accumulation of deficits across different physiologic systems (Rockwood et al., 2007), rather than to sarcopenia and other age-related modifications as the principal pathophysiological aspect (Fried et al., 2001).

Chronic Kidney Disease (CKD) is consistently associated with frailty or decreased physical function (Walker et al., 2013). According to a recent systematic review, the prevalence of frailty among stages 1-4 CKD ranges from 7% to 42.6% (Chowdhury et al., 2017), and it has been suggested that it may represent both a health outcome and an independent predictor of adverse outcomes in CKD (Afilalo et al., 2009).

Several risk factors including chronic inflammation, acidaemia, hormonal changes, and malnutrition might accelerate the development of frailty in CKD (Kojima et al., 2017), which is further exacerbated by a process of premature and accelerated ageing (Kooman et al., 2014).

Kooman et al., (2014) described the main mechanisms that could lead to premature ageing in CKD, which include an increase in allostatic load, mediated by oxidative stress and persistent inflammation, the activation of the stress resistance response and consequent alteration of the anabolic and catabolic responses, and the inevitable increase of pro-ageing factors such as hyperphosphatemia, angiotensin II, and accumulation of interstitial sodium. These risk factors would lead to the main features of premature ageing, namely muscle wasting and accelerated vascular disease (Kooman et al., 2014). The consequences of these pathophysiological features of premature ageing are that, regardless of age, CKD patients tend to have greater physical function deficits than otherwise healthy older adults (Painter et al., 2013), and that the prevalence of frailty in CKD is higher than in the healthy elderly population (Chowdhury et al., 2017).

In addition, it has been shown that lower estimated glomerular filtration rates (eGFR) are associated with a worse frailty status (Reese et al., 2013), meaning that the severity of CKD is associated with frailty in a graded manner. This relationship reflects how the progression of CKD could lead to worse physical function and, by the time one patient reaches CKD-5 and HD, he/she will be more likely to be frail than at the earlier stages.

Therefore, not surprisingly, the prevalence of frailty is higher in CKD-5 patients undergoing HD therapy compared to non-dialysis dependent CKD patients, with rates ranging from 14% to 73% (Chowdhury et al., 2017). Large observational studies have found that the prevalence of frailty in incident dialysis patients is very high (Johansen et al., 2007; Bao et al., 2012), and that dialysis initiation does not result in an improvement of frailty (Johansen et al., 2013). On the contrary, progression on dialysis seems to be associated with a further decrease of physical function (Kurella-Tamura et al., 2009).

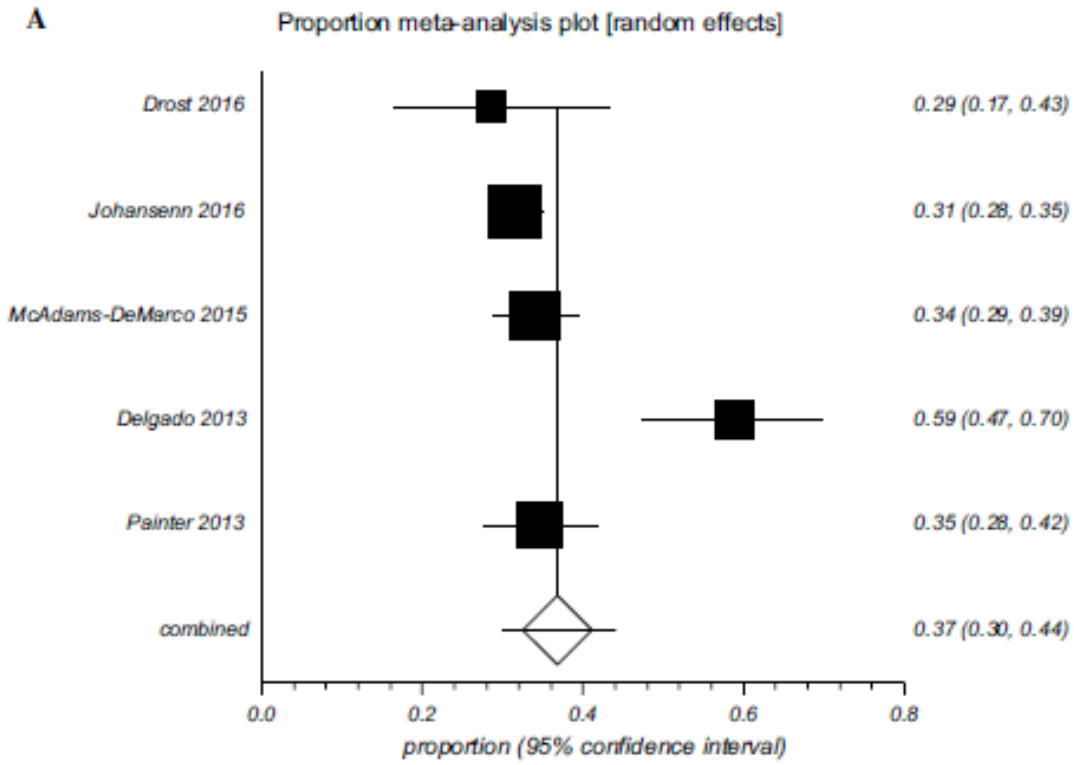
In addition, frailty in HD patients has been found to be independently associated with various adverse outcomes such as hospitalisations and mortality (Johansen et al., 2007; Bao et al., 2012; Alfaadhel et al., 2015; Lee et al., 2017), number of falls (McAdams-

DeMarco et al., 2013), cardiovascular disease (Kutner et al., 2014b), and lower cognitive function (McAdams-De Marco et al., 2015a).

The large discrepancy in frailty prevalence among HD populations reported in the current literature (Chowdhury et al., 2017) is at least partly attributed to the great heterogeneity of tools that have been used to measure frailty in the various studies. A systematic review on the frailty measurement tools in CKD found that the large majority (72%) of studies used the Fried's frailty phenotype, while the remainder investigations employed one or a combination of the frailty scales named above (Chowdhury et al., 2017). Another systematic review (Kojima et al., 2017) performed a meta-analysis by calculating the pooled prevalence of frailty, assessed by means of the Fried's frailty phenotype: what emerged from this research is that the prevalence of frailty was considerably higher when the frailty criteria were established by self-report rather than by objective measurements. More precisely, when the gait speed and strength components of frailty were assessed by means of an objective physical performance measure, the pooled prevalence of frailty was 36.8% (Figure 1.2), while when these two components were evaluated by means of a surrogate self-reported physical functioning measure (a score less than 75 in the physical function scale of the SF-36 quality of life questionnaire), the pooled prevalence of frailty was 67%, almost double than the objectively measured one. Although the estimates of objective/subjective frailty emerging from this meta-analysis may be biased, considering that the included studies were heterogeneous in terms of exact operationalisation of physical frailty (e.g. Delgado et al., 2013 employed physical function and activity scores under the lowest quintile as opposed to the standard Fried's cut-off values used in the other studies (Figure 1.2)), the findings raise the question as to whether a self-reported assessment of frailty may be a valid method in dialysis patients. Johansen et al., (2014) performed a comparison of self-reported and objective measurements of frailty, based on the frailty phenotype, in HD patients. The authors found that the self-reported assessment of frailty had a high sensitivity (90%), but only limited specificity (64%), and positive predictive value (54%). The implications of this are that an assessment of frailty based on objective measurements might be preferable to self-report evaluations in HD patients, due to the better accuracy of the first method. Nevertheless, self-reported definitions of frailty

have been shown to have a similar prognostic value to the objectively measured frailty phenotype, being strongly associated with negative health outcomes and mortality (Johansen et al., 2016). In light of this association, despite the lower accuracy, assessing frailty with self-report information might be more feasible in a clinical setting, where objective measures of frailty are not always available (Johansen et al., 2016).

Figure 1.2. Forest plot of prevalence of frailty in CKD-5 based on the Fried's phenotype (Kojima et al., 2017, p. 1994).



1.2.3.1 Modifiability of frailty in CKD-5

The question as to whether frailty can be modified or even reversed in the general population of older adults living in the community has been addressed by many randomised controlled trials (Cameron et al., 2013; Kim et al., 2015; Tarazona-Santabalbina et al., 2016; Liao et al., 2019). The results from these investigations have generally indicated that physical frailty, as assessed by means of phenotypic frailty (Fried

et al., 2001), can be at least partially reversed following exercise interventions (Travers et al., 2019). In particular, the components of weakness, slowness, low physical activity and exhaustion seem to be positively affected by multicomponent exercise programs involving strength, balance, aerobic and flexibility training (Kim et al., 2015; Tarazona-Santabalbina et al., 2016; Liao et al., 2019). Moreover, a recent systematic review concluded that a combination of protein supplementation and strength training is effective in delaying or reversing frailty in primary care (Travers et al., 2019).

There is still no consensus reached by the renal care community regarding the extent frailty may be preventable or reversible in HD patients and which treatment strategies may be more efficient and or effective. However, three main courses of intervention have been suggested to combat premature ageing and consequently frailty, namely the correction of the CKD-related pro-ageing factors (such as oxidative stress, inflammation, and hyperphosphatemia), physical exercise, and optimal nutrition (Kooman et al., 2014).

Even though there's no current direct evidence that the frailty status can be prevented or reversed by means of physical exercise in HD patients, a few studies have examined the effect of various kinds of exercise interventions on strength and physical function, which are core components of the frailty phenotype, and found promising results (Ling et al., 2003; Storer et al., 2005; Greenwood et al., 2012; Bullani et al., 2012; Kirkman et al., 2014). Although these encouraging findings do not constitute ultimate proof that frailty can be reversed, they certainly show that at least three out of five components of the Fried's frailty phenotype, i.e. low physical activity levels, poor strength, and low gait speed can be modified by means of an exercise intervention in HD patients, which is indirect evidence of the exercise-modifiable nature of frailty in this population. More recently, it has been suggested that, considering the physical activity barriers HD patients are exposed to (Johansen et al., 2010), pre-habilitation of frail patients approaching the start of dialysis might be a beneficial treatment strategy (Sheshadri et al., 2017).

Lastly, it should be acknowledged that kidney transplantation was found to be associated with an improvement of the frailty status 3 months after the transplant (McAdams-DeMarco et al., 2015b), which highlights indirectly how this treatment modality is generally the most preferred in the management of CKD-5 (Pesavento et al., 2009).

1.2.3.2 Physical function in CKD-5

Impaired physical function is one of the core components of the frailty phenotype, as both low gait speed and poor muscle strength are embedded in the operational definition of frailty provided by Fried et al., (2001). Several studies have reported various degrees of physical function impairment in CKD-5, with a few observational studies showing how physical function declines as a function of time in HD patients (Kurella-Tamura et al., 2009; Sutcliffe et al., 2018).

Kurella-Tamura et al., (2009) assessed the self-reported functional status in a large group of nursing home residents starting HD and repeated the assessment at 3 and 12 months from dialysis initiation: the results from this study are staggering, as only 39% of the patients taking part in the investigation preserved their functional status 3 months after starting dialysis, and only 13% preserved it at 12 months.

In a more recent study, Sutcliffe et al., (2018) analysed the degree of physical function deterioration in a smaller cohort of patients starting HD in Australia. The authors reported a 30% decrease in number of 30 seconds chair sit to stands, as well as a 9% increase in the timed-up and go test, meaning a deterioration of this kind of performance.

In addition, echoing the results from Kurella-Tamura et al., (2009), another recent investigation showed that, during a 2-year follow up, only 15.3% of prevalent HD patients maintained their (self-reported) physical function levels, and the trajectory of physical function deterioration was even more marked in patients aged over 75 years of age, with only 3.6% of these preserving their physical function after 2 years (van Loon et al., 2017).

Recent research has also focused the attention to the effects of different dialysis modalities on the physical function decline trend, suggesting that this latter is not influenced by the dialysis modality, as HD and peritoneal dialysis patients seem to have similar functional status (Iyasere et al., 2016; Painter et al., 2017).

The question as to how CKD-5 patients compare to healthy individuals in terms of physical function has also been addressed by a number of scientific reports. The values of peak oxygen uptake (VO_{2peak}), for instance, have been shown to be significantly reduced in CKD-5 patients, who in average score 60% to 70% of the age-predicted values (Johansen et al., 1999; Smart et al., 2011). In the context of CKD-5, a VO_{2peak} threshold

value of 17.5mL/min/Kg was shown to have important prognostic value, as strongly associated with survival (Sietsema et al., 2004), and very often HD patients present with VO_{2peak} values lower than this threshold (Kouidi et al., 1998). In addition, it has been pointed out that the actual VO_{2peak} of CKD-5 patients may be considerably lower than the results reported in the scientific literature, given that not all CKD-5 patients, especially HD patients, are eligible to undergo a peak exercise assessment due to severely limited mobility or to significant CVD (Painter, 2005).

Slow gait speed is a commonly reported component of frailty (Fried et al., 2001), and in HD patients it has been shown to be associated with mortality (Kutner et al., 2015) and increased number of hospitalisations (Kutner et al., 2014). Kutner et al., (2015) classified a large group of prevalent HD patients in different gait speed categories, and at least 24% of these patients presented with a gait speed slower than the threshold value indicative of frailty (Fried et al., 2001). In addition, smaller studies comparing gait speed in HD patients and healthy individuals suggest that HD patients have an 18% (Blake et al., 2004) to 34% (Johansen et al., 2003a) reduced self-selected gait speed compared to healthy subjects.

Low handgrip strength is another component of the frailty phenotype, which is indicative of poor muscle strength (Fried et al., 2001). A systematic review revealed that handgrip testing is extensively used in CKD-5 patients on HD, and that this kind of assessment is a valid tool for the prediction of clinical complications (Leal et al., 2011). This systematic review reported that the average handgrip scores for HD patients ranged from 12 to 38Kg in men, and 11 to 26Kg in women, and although it is difficult to extrapolate what percentage of these patients meet the frailty criteria of low handgrip strength, a few studies suggest that the average handgrip strength of dialysis patients may be lower than the threshold value indicative of frailty (Qureshi et al., 1998; Constantin-Teodosiu et al., 2002; Wang et al., 2005). In addition, studies comparing CKD-5 patients with the non-uraemic population suggest that handgrip strength is reduced by 26 to 51% in patients who are on dialysis (Stenvinkel et al., 2002; Wang et al., 2005, Silva et al., 2011). A recent study also reported that poor muscle strength, assessed by means of handgrip test, is an independent predictor of all-cause mortality in HD patients (Vogt et al., 2016).

A further measure of muscle strength commonly reported, in the context of physical function assessment in CKD-5, is lower limb strength assessed by means of dynamometry (Koufaki et al., 2010). Even though the lack of normative data limits the comparison of CKD patients with the general healthy population, a study by Johansen et al., (2003) reported that lower limb strength, as assessed by dynamometry, was approximately 22% lower than in non-uraemic control subjects. Conversely, Blake et al., (2004) reported a 45% lower limb strength in HD patients compared to a group of healthy individuals. The clinical and prognostic value of low muscle strength assessed by means of dynamometry has been the focus of recent investigations. Particularly, lower limb strength was found to be an independent predictor of slow gait (Abe et al., 2016) and increased mortality (Matsuzawa et al., 2014) in HD patients.

The ability to perform chair sit-to-stands has also been used commonly as a surrogate measure of lower limb function in the context of CKD (Painter et al., 2005). In a feasibility study, Painter et al., (2000) reported that chair sit-to stand testing in HD patients was significantly impaired (25% of healthy age-predicted values), while Blake et al., (2004) found a 28% lower sit-to-stand performance in HD patients compared to healthy controls. Interestingly, the 5 repetitions chair sit-to-stand test (CSTS-5) has been shown to have proven clinical value, as cut-off values of >15 seconds and >16.7 seconds have been found to be predictive of recurrent and injurious falls respectively (Buatois et al., 2008; Ward et al., 2015).

Analogously to the CSTS-5, the timed up and go test (TUG) has been described to have clinical value, as a time >14 seconds to perform this task has been shown to discriminate individuals with history of recurrent falls (Shumway-Cook et al., 2000). In addition, a cut-off value of >10 seconds was shown to be strongly associated with a higher degree of disability in activities of daily living in older HD patients (Cook et al., 2008). In this study, Cook and colleagues report a staggering 80% of patients unable to perform the TUG at all (7%) or under 10 seconds (73%) and, echoing these results, a study conducted on pre-dialysis patients revealed that the average time to perform the TUG in these patients was above the threshold value for greater functional disability (10 seconds) by 12% (Roshanravan et al., 2013).

Even though postural balance usually lies outside the domain of physical function assessment in CKD patients (Koufaki et al., 2010), an increasing number of studies on balance control, involving static posturography, have been conducted in CKD-5 patients in the last 5 years (Shin et al., 2014; Magnard et al., 2014; Zanotto et al., 2017). Shin et al., (2014), for instance, compared the static balance in a small group of HD patients with healthy controls, finding an increased postural sway in all the variables examined, with differences ranging from +22% to +139% in HD patients. Similarly, Magnard et al., (2014) reported increased postural sway, meaning worse balance control, in HD patients compared to healthy individuals. The significant differences in the variables examined ranged from +32% to +47% in the group of HD patients. Notably, Blake et al., (2004) had also found an increased postural sway (+33%) in a small group of HD patients compared to healthy subjects. Although the clinical utility of static posturography-based measurements of balance is still not recognized unanimously by the scientific community, some research has demonstrated the potential of this kind of assessment in discriminating recurrent fallers from non-fallers among elderly individuals (Bigelow et al., 2011).

In conclusion, the evidence of impaired physical function in the context of CKD-5, and among dialysis patients in particular, is overwhelming. The role of physical activity and exercise in improving physical function in these patients is equally overwhelming (Painter et al., 2005). Recent systematic reviews with meta-analysis highlighted how various modalities of exercise training have resulted effective in improving self-reported physical functioning, maximum oxygen consumption, the 6-minute walk test, lower limb muscle strength and quality of life (Heiwe et al., 2014; Sheng et al., 2014; Chung et al., 2017; Matsuzawa et al., 2017). In addition, some exercise intervention studies also suggest that exercise training can improve other physical function outcomes such as the TUG (Heiwe et al., 2001; Storer et al., 2005), the CSTS-5 (Manfredini et al., 2017), and postural balance (Frih et al., 2018) in CKD-5 patients.

1.2.3.3 Physical activity behaviour in CKD-5

Physical activity is another crucial component of the Fried's frailty phenotype (Fried et al., 2001), as low self-reported levels of physical activity is one of the criteria around

which frailty is operationalised and among all the frailty components, it is intrinsically the most exercise-modifiable.

In the last 20 years, several studies reported information on the physical activity patterns and/or behaviour of CKD-5 patients (Painter et al., 2000; Johansen et al., 2000; O'Hare et al., 2003; Tentori et al., 2010; Matsuzawa et al., 2012; Painter et al., 2017; Broers et al., 2017; Cupisti et al., 2017). These studies consistently documented that HD patients have significantly reduced levels of physical activity compared to age-matched non-uraemic individuals, which are indicative of marked sedentary behaviour (Johansen et al., 2010; Stringuetta-Belik et al., 2012; Matsuzawa et al., 2012). The clinical implications of these low physical activity levels involve multiple domains of health. For instance, global physical function is affected due to the well-known negative effects of sedentary behaviour on bone and skeletal muscle function (Kurella-Tamura et al., 2009), but also cardiovascular and mental health seem to be negatively influenced (Johansen et al., 2010; Tsai et al., 2017). Overall, sedentary behaviour has been linked to lower quality of life as well as to the development of adverse clinical outcomes such as hospitalisations, major cardiovascular events and mortality in CKD-5 patients (O'Hare et al., 2003; Tentori et al., 2010; Tsai et al., 2017).

Both subjective and objective assessments of physical activity have been widely employed to characterise physical activity or sedentary behaviour in the context of CKD-5. As expected, very large epidemiological studies such as the Dialysis Outcomes and Practice Pattern Study (DOPPS) and the Dialysis Mortality and Morbidity Study (DMMS) used self-reported measures of physical activity due to their higher feasibility. The results of these studies are comparable, as both studies highlighted how 35% to 44% of the dialysis patients from their cohorts never or almost never engaged in any kind of structured physical activity, with 38% to 42% of them having severe limitations in performing moderate physical activity (O'Hare et al., 2003; Tentori et al., 2010). In the same way, studies using standardised questionnaires, such as the international physical activity questionnaire (IPAQ), have shown that 27% to 40% of prevalent HD patients are completely inactive by self-report (Li et al., 2010; Stringuetta-Belik et al., 2012).

On the other hand, smaller studies, with sample sizes ranging from n= 24 to n= 202 (Mafra et al., 2011; Matsuzawa et al., 2012), used objective measurements of physical activity such as pedometers or uni-axial and tri-axial accelerometers. Similarly, studies aiming to compare the physical activity patterns of CKD-5 patients with those of healthy individuals also used objective measurements of physical activity, due to their greater precision and reliability. These studies have shown, with great variability, how HD patients present with reduced number of daily step counts (-26% to -164%) compared to healthy controls (Mafra et al., 2011; Broers et al., 2017). Typically, these studies have reported that HD patients take on average 2800 to 7100 steps per day, which is 29% to 72% less than the current recommendations for a healthy lifestyle (Tudor-Locke et al., 2004). Additionally, further studies involving objective measurements of physical activity have described reduced activity counts (-18% to -35%), greater time spent in sedentary activities (+15%), less time spent in moderate activities (-38%) and total energy expenditure (-25%) in HD patients compared to healthy individuals (Johansen et al., 2000; Agarwal et al., 2011; Cupisti et al., 2011; Baria et al., 2011; Broers et al., 2017).

Furthermore, the progression of dialysis-independent CKD to CKD-5 seems to be associated with a decrease in physical activity. This is supported by the finding that HD patients exhibit a significantly higher percentage of sedentary behaviour compared to stage 2-4 CKD patients (Agarwal et al., 2011), and also that dialysis initiation is associated with a decrease of self-reported and objective measurements of physical activity (Johansen et al., 2000a). This phenomenon can be explained partly by the increasing comorbidity and consequent progressive decline of physical function observed in CKD-5 patients (Kurella-Tamura et al., 2009), but also by the fact that HD therapy entails prolonged periods of sedentary behaviour due to the imposed sitting time during dialysis. The effect of HD therapy on physical activity behaviour has been object of many studies, involving objective measurements of physical activity, that consistently reported greater sedentary behaviour of CKD-5 patients during dialysis days compared to non-dialysis days (Panaye et al., 2015; Cobo et al., 2015; Gomes et al., 2015; da Costa Rosa et al., 2017).

1.2.3.4 Relationship of frailty, physical function, and physical activity with falls in CKD-5

Recent research has shown that frailty is associated with a 2.39-fold higher risk of history of falls (Kutner et al., 2014), and is predictive of a 3.09-fold higher number of falls (McAdams-DeMarco et al., 2013) in CKD-5 patients on maintenance HD. In addition, self-reported frailty has been shown to be associated with adverse outcomes arising from falls, such as a higher risk of fractures (Delgado et al., 2015). Consequently, these studies strongly suggest that impaired physical function and physical inactivity may be associated with falls, in the context of CKD-5, given that these domains contribute to operationalise frailty itself (Fried et al., 2001).

Nevertheless, only approximately 60% of the studies that investigated falls and their risk factors, in the CKD-5 population, reported either physical function or physical activity information relating to the falling status of these patients (Desmet et al., 2005; Cook et al., 2006; Rossier et al., 2012; McAdams-DeMarco et al., 2013; Farragher et al., 2014; Kutner et al., 2014; Polinder-Bos et al., 2014; Delgado et al., 2015; Wang et al., 2017; Kono et al., 2018), showing contrasting results. For instance, Desmet et al., (2005) found a significant association between poor walking performance and falls in their study, as failing to walk 10 meters was predictive of a 2-fold higher risk of falls. In more recent studies, low performance on the SPPB was also found to be associated with an increased risk of falling in HD patients (Wang et al., 2017; Kono et al., 2018). Additionally, Delgado et al., (2015) reported that self-reported physical function was associated with a 33% higher risk of time to first fall or fracture in a large cohort of incident dialysis patients.

In contrast with these studies, other research did not find any relationship between physical function and falls in HD patients. Particularly, Cook et al., (2006) found no significant differences in the level of dependency required in activities of daily living, nor in TUG performance between fallers and non-fallers. Similarly, Polinder–Bos et al., (2014) also did not find any differences in self-reported limitations in the ADLs between HD patients with and without falls, while Farragher et al., (2014) did not find significant differences in TUG between fallers and non-fallers (although fallers had a lower

performance amounting to -12.8% compared to non-fallers) in a small cohort of peritoneal dialysis patients.

In addition to these findings, a few studies reported some significant differences in physical function between patients with positive falling status and patients who were falls-free that did not quite reach statistical significance in multivariate, adjusted-models. For instance, Desmet et al., (2005) reported that in univariate analysis, compared with non-fallers, HD patients with falls had a significant lower performance in rising from a chair (-34.9%), in maintaining standing balance with eyes closed (-22%), and in the one-leg standing balance test (-22.9%). These differences were no longer significantly associated with increased odds of falling in multivariate logistic regression analysis (Desmet et al., 2005). Analogously, Rossier et al., (2012) assessed physical function in a small cohort of HD patients by means of the POMA, and determined the incidence of severe falls prospectively in these patients. The baseline comparison of fallers vs non-fallers indicated that fallers had a significant lower POMA score compared to non-fallers (-9.3%), although no significant association was found in the logistic regression model designed for the prediction of falls, and the authors concluded that a lower POMA score was not associated with falling in HD patients (Rossier et al., 2012). More recently, Wang et al., (2017) reported a significant lower ankle dorsiflexion muscle strength in HD patients who reported falls at 12 months compared to those who did not. However, the multivariate negative binomial regression analysis did not reveal any significant association between lower muscle strength and number of falls experienced by study participants.

Only one study explored the relationship between physical activity and falls in dialysis patients (Delgado et al., 2015). This study highlighted that three components of frailty, namely poor physical function, exhaustion, and physical inactivity had similar association estimates with falls or fractures (HR 1.33, 95% CI 1.01 – 1.75; HR 1.40, 95% CI 1.10 – 1.76; HR 1.36, 95% CI 0.78 – 2.37). Nevertheless, only the first two components reached statistical significance in the fully adjusted Cox proportional hazards model, and the authors concluded that self-reported physical activity was not predictive of falls or fractures in the study cohort (Delgado et al., 2015).

In conclusion, although the current body of evidence strongly suggests that frailty is associated with falling in CKD-5 patients (McAdams-DeMarco et al., 2013; Kutner et al., 2014; Delgado et al., 2015), very little information on the relationship between the single frailty domains of low physical function/activity and falls is currently available. Approximately 40% of the studies investigating the risk of falling in HD patients did not include physical function/activity assessments at all as potential risk factors for falls (Roberts et al., 2003; Cook et al., 2005; Roberts et al., 2007; Abdel-Rahman et al., 2011), while other studies only included self-reported measurements of physical function/activity (Polinder-Bos et al., 2014; Delgado et al., 2015), which are generally considered less reliable than objective measurements (Overend et al., 2010; Ahn et al., 2015). As far as the remaining studies are concerned, the results are ultimately inconclusive as only a few studies found a significant association between objective physical function measures and falls among CKD-5 patients (Desmet et al., 2005; Wang et al., 2017; Kono et al., 2018), while others did not show any significant association (Cook et al., 2006; Farragher et al., 2014).

Because physical function/activity are potentially exercise-modifiable components of frailty, establishing which physical function/activity measures may be more closely associated with falls, if any, is of paramount importance, as this would eventually allow to tailor exercise-based rehabilitation programs aimed to reduce the occurrence of falls in CKD-5 patients on HD.

1.2.4 Cardiovascular disease in CKD-5

CKD has been consistently shown to constitute an independent risk factor for the development of cardiovascular disease (CVD) (Rucker et al., 2009). CVD is the leading cause of death in CKD-5 patients, accounting for approximately 40% of deaths in dialysis patients (USRDS, 2011), and cardiovascular mortality in dialysis patients is estimated to be 10-fold to 100-fold higher than in age and sex-matched people in the general population who are free from kidney disease (Foley et al., 1998). The incidence and prevalence of CVD in patients affected by CKD is high and the most common clinical manifestations

encompass stroke, coronary artery disease/myocardial infarction, congestive heart failure and atrial/ventricular arrhythmias (Parfrey et al., 1999; Tonelli et al., 2016).

The risk of cerebrovascular accidents is increased among all categories of CKD, and particularly so in CKD-5: the relative risk of stroke in CKD-5 patients is about 5 to 10 times higher than the relative risk of their non-uraemic, age-matched counterparts. This magnitude of risk is even higher than that of coronaropathy, as the relative risk of myocardial infarction in CKD-5 patients is 2.5- to 3 times higher than in general population (Toyoda et al., 2014). Nevertheless, it should be acknowledged that the epidemiology of coronary disease is confounded by the common co-existence of CKD and diabetes, which is a further well-known independent risk factor of myocardial infarction.

Congestive heart failure is also a common complication of CKD, and its clinical manifestation is particularly evident in the more advanced stages of kidney dysfunction (prevalence 31-36% in dialysis patients), due to the compromised renal excretion of water and sodium, or to the primary cardiac dysfunction (Tonelli et al., 2016).

Finally, sudden cardiac death, defined as any sudden, unexpected death attributable to cardiac aetiology, and generally occurring with little or no warning at all, is one of the main causes of death among CKD-5 patients on dialysis. It is estimated that about 20 to 25% of deaths among all dialysis patients are due to sudden cardiac death (Whitman et al., 2012).

The traditional risk factors implicated in the development of CVD include hypertension, diabetes mellitus, dyslipidemia and albuminuria: many of these are increased in CKD-5 patients, and mainly hypertension, hyperlipidemia, and diabetes seem to be implicated in the aetiology of CVD in these patients (Parfrey et al., 1999). Some of these traditional risk factors of cardiovascular mortality such as hypertension, obesity and dyslipidemia seem to have a reverse epidemiology in HD patients. Systolic blood pressure, for instance, present a U-shape relationship with mortality, as both high and low blood pressure are associated with increased mortality (Tonelli et al., 2016).

So in the same way, dyslipidemia seems to have the same kind of relationship with mortality (Kasiske et al., 1998). Inflammation seems to play a determinant role in this

relationship, as dialysis patients without evidence of inflammation have a positive relationship between cholesterol and cardiovascular or all-cause mortality, while those with signs of inflammation display a U-shape relationship between serum cholesterol and cardiovascular mortality. This seems to suggest that low cholesterol levels may reflect states of inflammation and malnutrition (Kasiske 1998).

Obesity, on the other hand, represents a different model of reverse epidemiology. The obesity paradox in CKD-5 has been recently described and seems to be responsible for the abnormal relationship between increased body weight and mortality: the paradox is that the chances of longer survival are better in patients who have a higher BMI compared to those who have a lower BMI, probably due to haemodynamic stability, protein-energy wasting modulation, and sequestration of uraemia-related toxins in the adipose tissue (Park et al., 2014).

In addition to the traditional risk factors, CKD patients are also exposed to additional risk factors involved in the pathophysiology of CVD (Figure 1.3). These factors often result from the CKD-related uraemia, which can lead to the accumulation of toxins that are detrimental for cardiac function (Tonelli et al., 2016), and they encompass altered metabolism of phosphorus and calcium, anemia, chronic inflammation and oxidative stress, proteinuria, and hyper-homocysteinemia. Furthermore, dialysis patients might have additional potential risk factors such as extracellular fluid volume overload, and bacteremia compared to patients who do not depend on dialysis (Rucker et al., 2009).

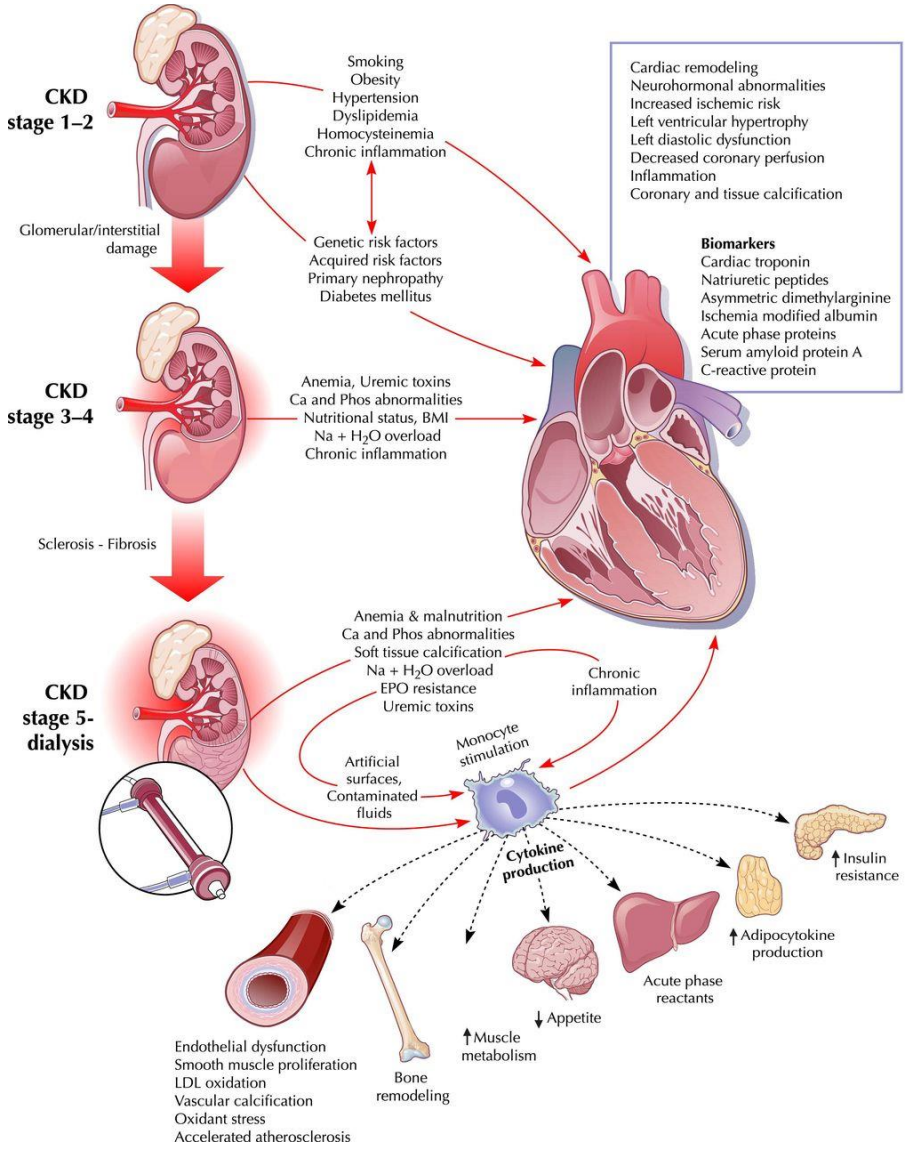
These CKD-related risk factors can contribute to the development of CVD by increasing vascular stiffness in particular. The stiffening of the arterial walls, especially in the large arteries, constitute one of the main risk factors for CVD and is due to multiple factors, whereas vascular calcification represents one of the main causes. More precisely, vascular calcification contributes to CVD by inducing myocardial ischemia, microvascular damage in the brain and in the kidney, and cardiac hypertrophy (London, 2011). Vascular calcification is an active process which involves differentiation of contractile vascular smooth muscle cells, and other endothelial cells into ‘osteoblast-like’ cells, and has been shown to be activated by a multiplicity of factors including cellular senescence, oxidative stress, dyslipidemia, glycation by-products, and hyperphosphatemia (Tonelli et al., 2016).

In the context of CKD, and CKD-5 in particular, vascular calcification seems to be promoted by the abnormal calcium and phosphate homeostasis, which is associated with the alteration of the endocrine pathway involving the parathyroid hormone, and the vitamin D-fibroblast growth factor-23—Klotho axis (London, 2011; Kusano et al., 2011). In the context of CKD however, vascular stiffness is also promoted by endothelial dysfunction, a well-documented feature of this clinical population (Moody et al., 2012). Impaired endothelial function can negatively impact on CVD not only via vascular stiffness, but also by promoting atherosclerosis and, consequently, coronary artery disease (Hirata et al., 2014). Carbamylation is one of the mechanisms that have been suggested to promote endothelial dysfunction in CKD (Tonelli et al., 2016). This is a chemical reaction wherein the accumulating urea in the bloodstream dissociates to form cyanate, which would then react irreversibly with free amino groups and other proteins (Tonelli et al., 2016). Further CKD-related mechanisms involved in endothelial dysfunction are the decrease in number of endothelial progenitor cells, which play an important role in repairing the vascular endothelium, and the uraemic-related accumulation of indoxyl sulfate which would accelerate the arteriosclerosis process (Kusano et al., 2011). Moreover, since the kidney is a main source of antioxidant enzymes, the deterioration of renal function would inevitably result in the increase of pro-oxidant factors, which are known markers of cardiac risk (Tonelli et al., 2016). Analogously, the atherogenesis process has been described to be accelerated by some CKD-related inflammatory particles such as calciprotein particles, cholesterol crystals, and inflammasomes (Swaminathan et al., 2011).

The combined effects of vascular stiffness and chronic inflammation are also known to affect left ventricular hypertrophy (Graham-Brown et al., 2017), one of the most common features and risk factors involved in the pathophysiology of CVD in people living with CKD (Major et al., 2018). Particularly, left ventricular hypertrophy can lead to a cascade of adverse cardiovascular events including malignant arrhythmias and sudden cardiac death (Makar et al., 2017), left atrial dilatation with atrial fibrillation (Franczyk et al., 2016), and heart failure (Di Lullo et al., 2015).

In addition to risk factors described above, it should be acknowledged that the worsening of renal functioning is also associated with a chronic activation of the renin–angiotensin system or sympathetic nervous system, which is thought to accelerate cardiovascular disorders. As kidney function deteriorates, the primary hypertension and sympathetic over-activation contribute in a synergic manner to the development of CVD by increasing the cardiac strain (Kusano et al., 2011).

Figure 1.3. Pathophysiological interactions between CKD and CVD (Ronco et al., 2008, p. 1534).



1.2.4.1 Autonomic dysfunction in CKD-5

The progressive decline of renal function is associated with impaired cardiovascular autonomic control (Bavanandan et al., 2005). Adequate autonomic control is fundamental for the compensatory regulation of blood pressure, and the chronic over-activation of the sympathetic nervous system plays a central role in the pathogenesis of hypertension, heart failure, and sudden cardiac events (Malpas, 2010).

Kidney damage can result in sympathetic overactivity by triggering afferent nerve traffic to the hypothalamus, where the centers of sympathetic control reside, via the spinothalamic tract. Even though the physiologic mechanisms activating the afferent nerve traffic are not completely understood, signals such as hypoxia, renal ischemia, adenosine, and angiotensin II seem to be implicated in triggering the sympathetic response (Vonend et al., 2008). Additional mechanisms that have been proposed to elicit sympathetic overactivity in CKD encompass the accumulation of asymmetric dimethylarginine, a compound that inhibits nitric oxide, thus promoting sympatho-excitatory effects, and the impairment of baroreflex function (Grassi et al., 2012).

A variety of direct and indirect measurements have been used for the assessment of cardiac sympathetic nervous system activity in CKD. Traditional techniques such as plasma norepinephrine levels and catecholamines turnover revealed contradicting data, as reported by a review of Rubinger et al., (2013), with studies reporting both lower and higher levels of catecholamines in CKD-5 patients.

Direct measurements of sympathetic nervous system activity such as regional norepinephrine spillover and efferent post-ganglionic muscle sympathetic nerve activity might be preferable to the classical techniques involving measurements of plasma norepinephrine levels, and have consistently been indicative of increased sympathetic activity in CKD-5 patients compared to non-uraemic populations (Rubinger et al., 2013). Nevertheless, these techniques have reduced applicability in CKD-5 patients, or may be less available in a clinical context. For instance, the norepinephrine spillover technique requires catheterisation and tracer infusions, and therefore its use is limited in HD patients, while the efferent post-ganglionic muscle sympathetic nerve activity has only been object of few studies due to its limited availability in clinical settings (Rubinger et al., 2013). For

this reason, indirect assessments of sympathetic activity have found higher applicability in CKD-5 patients on HD.

These indirect assessments of autonomic function are based on non-invasive beat-to-beat analysis of heart rate and blood pressure oscillations, and mainly consist of heart rate variability and baroreflex function, as assessed by means of baroreflex sensitivity, and baroreceptor effectiveness index (Parati et al., 2003).

1.2.4.2 Heart rate variability

Heart rate variability (HRV) can be described as the difference between the longest and the shortest R-R intervals within a predetermined test period (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

The assessment of HRV can be categorised into time-domain methods or frequency-domain methods. In the time-related method, the variables are derived from the calculation of inter-beat intervals during predefined recording periods. Measures such as mean heart rates, average duration of R-R intervals, and difference between the longest and shortest R-R intervals belong to this kind of method. The most common variable of the time-domain method is the standard deviation of the total number of R-R intervals between QRS complexes following depolarisation of the sinus node. These intervals are named normal to normal (NN) intervals, and therefore the variable takes the name of SDNN (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

The frequency-domain method consists of the spectral analysis of heart rate oscillations, in a given time of interest, and is usually presented as a three-dimensional diagram. This kind of analysis is classified as frequency-based because it allows the detection of both slow and rapid fluctuations of heart rate in predefined periods of time, which reflect the haemodynamic adjustment to changing cardiovascular demands. In particular, the spectral analysis identifies a low-frequency (LF) component, which is thought to derive from neural mechanisms related to vagal and sympathetic outflows, as well as a high-frequency (HF) component, representing respiration-mediated and vagally-dependent fluctuations of

R-R intervals (Parati et al., 1995). The ratio of the two components (LF/HF ratio) is commonly used as a measure of sympatho-vagal balance (Norton et al., 2005).

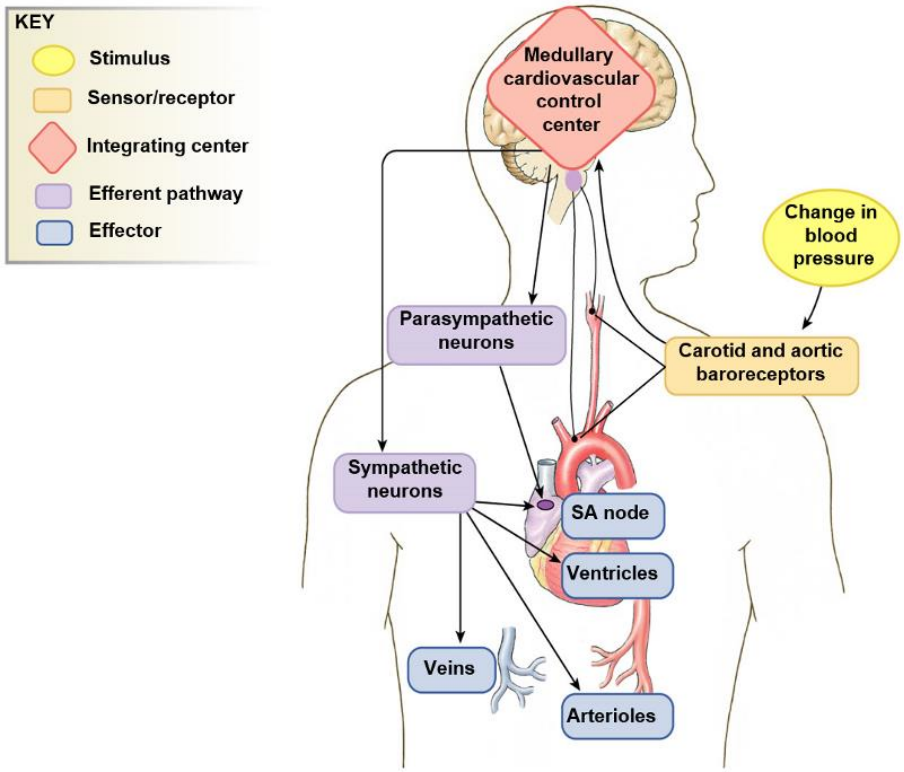
The studies that have investigated HRV in HD patients have consistently reported that this measure of autonomic function is decreased: both the LF and HF components were found to be lower than in non-uraemic individuals (Rubinger et al., 1999), while an increase in the LF/HF ratio was believed to represent an impairment of the autonomic function due to the shift towards a sympathetic predominance (Giordano et al., 2001). In addition, suppressed HRV is thought to convey prognostic value, as it was associated with increased cardiac mortality (Hayano et al., 1999; Fukuta et al., 2003). It should be acknowledged that a significant limitation of this kind of assessment, and of indirect measurements of autonomic function in general, is the limited applicability of this technique in those patients who present multiple ectopic beats, as the HRV variables are calculated in the context of NN intervals (La Rovere et al., 2008).

1.2.4.3 Baroreflex function

The baroreceptor reflex, or baroreflex, is one of the main physiologic mechanisms that control the cardiovascular and haemodynamic responses to short-lived or more sustained physical tasks such as changes in body position or exercise. The main role of the baroreflex is that of stabilising arterial pressure in response to perturbations of the circulatory homeostasis, which is achieved by various neuronal regulatory adjustments (Stauss, 2002). The baroreflex is regulated by specialised blood pressure sensors (baroreceptors), located in the aortic arch and in the carotid sinuses, which detect variations in the pressure load (Figure 1.4). These baroreceptors are sensitive to the arterial pressure by detecting the extent of stretch in the aorta and in the carotid arteries, and they provide the central nervous system with beat-to-beat information on the systemic blood pressure (Lanfranchi et al., 2002). More specifically, the baroreceptors provide an excitatory input to the neurons located in the nucleus of the solitary tract, which represents the brain stem centre for afferent baroreflex inputs (Zhang et al., 2000), while the rostral ventrolateral medulla is the centre for the efferent modulation of the baroreflex. When the baroreceptors detect a rise in arterial blood pressure the baroreflex produces sympathetic

inhibition and parasympathetic activation, which in turn results in decreased heart rate and vascular resistance (Pang, 2001). When a drop of blood pressure is sensed, the baroreflex triggers the opposite response, namely an increase in heart rate and vascular resistance. Increasing evidence suggests that this physiological mechanism is impaired in CKD, and that it might predict cardiovascular risk and all-cause mortality (Hildreth et al., 2012). The baroreflex function is typically assessed by measuring the sensitivity of the reflex, also known as baroreceptor reflex sensitivity, and the baroreceptor effectiveness index (Di Rienzo et al., 2001; Taylor et al., 2001; Stauss, 2002, Lanfranchi et al., 2002).

Figure 1.4. Baroreceptor reflex.



1.2.4.4 Baroreflex sensitivity

The baroreflex sensitivity (BRS) can be defined as the magnitude of baroreflex response per unit of blood pressure deviation from the operating point, whereas the operating point

represents the blood pressure at which the baroreflex responds most effectively to variations of arterial pressure (Stauss, 2002).

The first introduction and calculation of BRS was obtained by assessing the heart rate responses to perturbations of blood pressure provoked by the injection of vasoactive medications with minor effects on the sinus node (Smyth et al., 1969). This methodology is the so-called pharmacologic approach, which basically consists of administrating a vasoconstrictor drug, typically phenylephrine (Mortara et al., 1997), to measure the produced bradycardia. In this kind of assessment, the administration of the drug is performed during simultaneous and continuous recordings of beat-to-beat blood pressure and electrocardiography (ECG). The quantification of BRS is therefore obtained by calculating the slope of the regression line of the blood pressure and R-R interval responses, and is usually expressed as the variation in R-R interval in milliseconds (ms) per millimeters of mercury (mmHg) change in systolic blood pressure (La Rovere et al., 1998). Due to the fact that this method implies cannulation, its applicability is limited in some instances, thus, overtime, non-invasive methods of assessing BRS have been developed.

Within the non-invasive assessment tools of BRS, techniques such as the Valsalva maneuver and the neck chamber techniques are based on provoking abrupt changes of blood pressure, while another category of techniques are based on the analysis of spontaneous variations (unprovoked) of blood pressure and heart rate. The Valsalva maneuver and the neck chamber techniques follow the same principle of the pharmacologic approach, namely performing a concomitant measurement of beat-to-beat arterial pressure and R-R intervals while a substantial change in blood pressure is being provoked. In the Valsalva maneuver technique, this abrupt modification of blood pressure is triggered by the elevation in intra-abdominal and intrathoracic pressure caused by the forced expiration while the glottis is being kept closed (Palmero et al., 1981). Conversely, in the neck chamber technique, the variation of blood pressure is provoked through the selective modulation of the baroreceptors located in the carotid sinuses by applying a positive or negative pneumatic pressure to the neck of the patient. Particularly, neck

suction seems to be the most favourable technique, as this kind of pressure seems to be better tolerated by the patient (Eckberg et al., 1975).

The least invasive assessment of BRS is based on the analysis of spontaneous variations of blood pressure and heart rate. This approach is based on the observation that the activation of the baroreflex is not solely dependent on abrupt variations of systemic blood pressure, but it is also activated by small pressure changes that occur continuously throughout the day (La Rovere et al., 1998). The most utilised method based on the analysis of spontaneous variations of blood pressure and heart rate is the so-called "sequence method" (Pinna et al., 2015). This method is based on the same principles of the previous methods, namely that an increase in arterial blood pressure will generate a lengthening of the R-R interval and vice versa, and consists of continuous and simultaneous recording of beat-to-beat systolic blood pressure and heart rate by means of ECG and plethysmography (Pinna et al., 2000). During these recordings, a "sequence" is identified as a concomitant change in systolic blood pressure and R-R interval, of respectively 1 mmHg and 4 ms (Parati et al., 2000), for a minimum of three consecutive cardiac cycles, and it represent a baroreceptor regulatory event (Parati et al., 1988). The sensitivity of the baroreflex is therefore assessed by calculating the slope of the regression line relating variations in systolic blood pressure to variations in the R-R interval. Finally, the calculated slopes are averaged to compute the BRS (La Rovere et al., 2008).

The increasing popularity of this method is due to the fact that it is low-cost and inherently simple since it doesn't require provocation of an abrupt change in blood pressure (La Rovere et al., 2008). In addition, the sequence method has been shown to have the same prognostic value of the invasive methods to assess baroreflex function, such as the phenylephrine method (Pinna et al., 2000), high reproducibility (Parati et al., 2003) and moderate to good absolute and relative reliability (Maestri et al., 2009). Moreover, compared to other methods based on the analysis of spontaneous oscillations of blood pressure and heart rate, such as the spectral methods (La Rovere et al., 2008), the sequence method reduces the artefact effects of ectopic beats on the calculation of BRS, by imposing strict constraints on the concomitant change in systolic blood pressure and R-R interval (Pinna et al., 2015). For this reason, the sequence method may be preferable for the

assessment of baroreflex function in those patients who have a higher degree of cardiovascular disease and consequently it has been used extensively in CKD-5 patients on HD therapy (Studinger et al., 2006; Johansson et al., 2007; Sapoznikov et al., 2010; Sapoznikov et al., 2013; Gupta et al., 2016).

Several studies have reported that BRS is impaired in CKD (Gerhardt et al., 1999; Gao et al., 2005; Studinger et al., 2006; Johansson et al., 2007) and the degree of impairment may increase as the severity of CKD progresses, even if it's still unclear at which stage of disease the BRS starts to deteriorate (Hildreth et al., 2012). Although clear normative BRS data are currently not available in CKD-5 patients, Studinger et al., (2006) observed a markedly reduced BRS (-157%), assessed by means of the sequence method, in HD patients compared to healthy controls.

The aetiology of impaired BRS, and baroreflex function in general, is still unknown fundamentally. Nevertheless, it has been suggested that the deterioration of this reflex, in the context of CKD, may involve neuropathy of the peripheral nerves and reduced arterial distensibility in proximity of the carotid sinuses and in the aortic arch, that could lead to increased thresholds of baroreceptors activation and therefore to an impaired capacity of regulating blood pressure (Johansson et al., 2007). This last hypothesis seems to be supported by the observation that impaired BRS was found to be associated with arterial stiffness (Gupta et al., 2016) and vascular calcification (Chesterton et al., 2005). Johansson et al., (2007) conducted a prospective observational study aimed to determine whether baroreflex function, assessed by means of BRS and baroreceptor effectiveness index, had prognostic value in CKD patients. The results from this study indicated that BRS was an independent predictor of cardiac death among these patients. Even though the exact mechanisms by which impaired BRS could contribute to increased cardiovascular mortality are fundamentally unknown, it has been speculated that poor BRS may be implicated in the HD-related hypotension, which is a significant cause of death in HD patients (Chesterton et al., 2010).

1.2.4.5 Baroreceptor effectiveness index

In 2001, Di Rienzo et al., (2001) introduced a new parameter to assess the baroreflex by analysing the spontaneous oscillations of blood pressure and heart rate through the sequence method: the authors named this parameter baroreceptor effectiveness index (BEI).

The introduction of this measure originated from the observation that BRS quantifies exclusively the magnitude of the baroreflex, by analysing the slope of the regression line between systolic blood pressure and R-R intervals of the so-called baroreceptor sequences (Parati et al., 1988). Parati et al., (1988) had already observed that, during 24-hour recordings of blood pressure and heart rate, the study participants had a number of blood pressure ramps that were not coupled with a concomitant variation of the R-R interval. Therefore, even though a healthy person could appear to have a normal baroreflex function, as assessed by means of BRS, the presence of uncoupled blood pressure ramps may be suggestive of a reduced capacity of maintaining the arterial pressure homeostasis effectively through the baroreflex. Consequently, the BEI was introduced as a measure of how often the baroreflex is effective in driving the heart rate in response to perturbations of systolic blood pressure (Di Rienzo et al., 2001). Analogously to BRS, this index is obtained by means of the sequence method: a simultaneous change in systolic blood pressure and R-R interval for a minimum of three consecutive cardiac cycles is classified as a baroreceptor event. These events can be defined as “down-events”, which occur when a decrease in blood pressure is coupled with a shortening of the R-R interval, or as “up-events”, which occur when a rise in blood pressure is coupled with a lengthening of the R-R interval. The total events count is then obtained by summing the number of down-events and up-events recorded within a given time interval, and the BEI is derived by calculating the ratio of the total number of baroreceptor events and the total number of blood pressure ramps, regardless of whether these ramps are coupled or not with a change of the R-R interval (BEI= total n° of baroreceptor events/ total number of systolic blood pressure ramps) (Di Rienzo et al., 2001). The specificity of this tool was also assessed by Di Rienzo et al., (2001): the authors reported a reduction in BEI of approximately 89% in cats following surgical denervation of the aortic baroreceptors. Higher scores of BEI are

therefore indicative of a better regulatory response of the baroreflex and, in healthy individuals, the normal values of BEI range around 0.58±0.2 (Pitzalis et al., 2003).

Although the majority of clinical studies conducted on CKD-5 patients assessed baroreflex function by means of BRS, given its earlier introduction (Parati et al., 1988), BEI has also been shown to be reduced in CKD-5 patients compared to healthy subjects (approximately -48%) and to have prognostic value by Johansson et al., (2007), who concluded that reduced BEI was an independent predictor of all-cause mortality in CKD patients. In light of these findings, and considering the low costs and non-invasiveness of this measurement, BEI has increasingly become more popular as a complementary measure of baroreflex function and autonomic function in CKD patients (Rubinger et al., 2013), and some have suggested that this measure should be implemented as part of the tests currently used to stratify sudden cardiac death risk in HD patients (Franczyk-Skóra et al., 2015).

1.2.4.6 Relationship of baroreflex function and orthostatic blood pressure with falls

The deterioration of baroreflex function in CKD may be one of the mechanisms that affect the regulation of blood pressure in resting conditions (Rubinger et al., 2013), but also in the upright position or during the transition from a seated/supine position to upright standing. In normal conditions, the baroreflex ensures an efficient regulation of blood pressure during orthostasis because the relationships between arterial blood pressure, heart rate, respiration and sympathetic nerve activity shift or reset when upright, preventing hypotension and brain hypoperfusion by improving the cardiac output through increased heart rate, sympathetic activation and the respiratory-abdominal pump (Schwartz et al., 2012).

Mattace-Raso et al., (2007) conducted a large observational study aimed to examine the association between arterial stiffness, baroreflex function, and changes in blood pressure during an orthostatic challenge. The results from this study, conducted in older adults, showed that individuals with lower BRS had a more prominent drop of blood pressure during the orthostatic challenge. A drop in blood pressure is one of the factors that could lead to dizziness symptoms and potentially to falls (Post et al., 2010), as orthostatic

hypotension, along with carotid sinus hypersensitivity, is portrayed as one of the main cardiovascular disorders that can cause falls or syncope (Task force on syncope, European Society of Cardiology, 2004). Interestingly, the relationship between orthostatic hypotension and falls has been object of debate in the last five years. Although this cardiovascular condition is intuitively linked to an increased risk of falling (Brignole et al., 2004), a systematic review of the association between cardiovascular disorders and falls highlighted inconclusive evidence of a positive relationship between orthostatic hypotension and falls (Jansen et al., 2016). The authors of this review concluded that methodological heterogeneity of the studies included, and in particular the lack of standard definitions of orthostatic hypotension, was largely responsible for this non-finding. For instance, Finucane et al., (2014) reported that, in a large population of people aged ≥ 50 years living in the community, the prevalence of initial orthostatic hypotension (occurring within first 15 seconds) was about 33%, while only about 7% of the population met the canonical definition of orthostatic hypotension (Brignole et al., 2004) after one minute of standing. Because the systematic review by Jansen et al., (2016) included mainly studies wherein orthostatic hypotension was diagnosed after the first minute of orthostatic challenge, the authors concluded that the small proportion of studies revealing a positive association between orthostatic hypotension and falls may be explained by this definitional artefact. In addition, it has been pointed out that lack of apparent association between orthostatic hypotension and falling may also result from employing logistic analyses rather than time-to-event analyses, which would be more appropriate in light of the multifactorial aetiology of falls (Frith 2017). More recently, Mol et al., (2019) performed a systematic review with meta-analysis of all cross-sectional and longitudinal studies reporting on the association between orthostatic hypotension and falls. The authors concluded that this cardiovascular disorder is positively associated with falls (OR: 1.73, 95% CI: 1.50-1.99) in community-dwelling older adults. It is therefore possible that this recent publication may finally put an end to the long-lasting debate on orthostatic hypotension and falls (Frith 2017).

It should also be acknowledged that other investigations focused on the blood pressure changes to orthostasis, as a potential risk factor for falls, without necessarily introducing

the concept of orthostatic hypotension. For instance, two studies examined the relationship between blood pressure changes during orthostasis and falls in older adults (Heitterachi et al., 2002; Shaw et al., 2015). Heitterachi et al., (2002), conducted a prospective investigation aimed to explore the relationship between the short-term regulation of blood pressure during an orthostatic challenge, consisting of head up tilting to 60° for 3 minutes, and the incidence of falls over a 12 month period. The results from this study revealed that the magnitude of decreases in systolic blood pressure during 3 minutes of upright tilting was associated with a two-fold increased risk of falling. More recently, Shaw et al., (2015) conducted a similar study which involved an orthostatic challenge consisting of a passive transition from a seated position to upright standing. The authors concluded that subjects with a history of falls had a larger decrement of systolic blood pressure during the 3-15 minute period of orthostasis (Figure 1.5).

Another important finding that may link impaired baroreflex function, the homeostasis of blood pressure and falls is that high arterial pulse wave velocity, a measure of arterial stiffness, was found to be associated with falls in a large cohort of community-dwelling older adults (Wong et al., 2014). Increased arterial stiffness is one of the mechanisms thought to cause impairment of the baroreflex by increasing the thresholds of baroreceptor activation, which could lead to a decreased capacity of regulating blood pressure (Johansson et al., 2007; Hildreth et al., 2012), and potentially to cerebral hypoperfusion during orthostasis or during the transition from a resting position to upright standing (Wong et al., 2014).

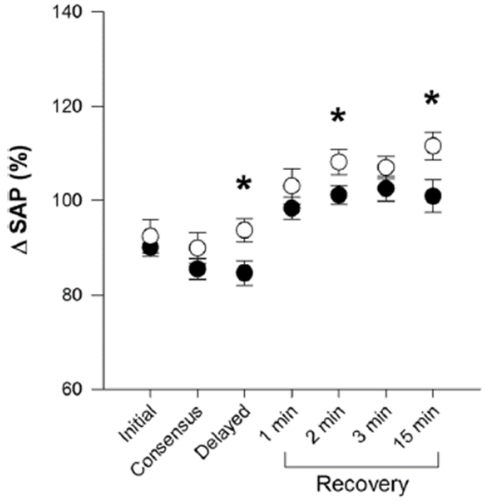
In addition, it should also be acknowledged that CVD may increase the risk of falling not only via cerebral hypoperfusion but also by impairing skeletal muscle function (Keng et al., 2019). For instance, heart failure, a highly prevalent comorbidity in HD patients, can aggravate muscle wasting due to the fact that exercise capacity is clinically reduced in people living with this condition (Fulster et al., 2013). Analogously, peripheral arterial disease can also negatively impact on physical function and skeletal muscle mass as a result of the restricted blood supply to the leg muscles (King et al., 2015; Harwood et al., 2017). Moreover, vascular disease is also linked to impaired cognition, a recognized risk

factor for falls (Rubenstein et al., 2006), through microvascular damage of the small cerebral vessels (Bronas et al., 2017).

In CKD-5 patients, a further component of risk for dizziness and pre-syncopal symptoms is also represented by the extensive use of antihypertensive medications such as alpha/beta blockers, and angiotensin-converting enzyme inhibitors (Post et al., 2010), which are commonly prescribed to counteract hypertension, one of the main clinical goals in the management of CKD (Lees et al., 2015). The use of this class of medications has been shown to be strongly associated with the risk of serious fall injuries in a large cohort of older people (Tinetti et al., 2014).

Despite the overwhelming evidence that baroreflex function is impaired in CKD-5 patients and that the risk of dizziness and falls is high in these patients (Roberts et al., 2003), no research has explored the relationship between the baroreflex, the cardiovascular responses to orthostasis, and falls in CKD-5 patients yet. Physical exercise has been shown to improve baroreflex function, assessed by means of BRS and BEI, in HD patients (Petraki et al., 2008). Therefore, if a positive association was to emerge between baroreflex function and falls, rehabilitation programs aimed to restore baroreflex function could be developed and implemented in the context of falls prevention in these patients.

Figure 1.5. Response of systolic arterial pressure (SAP) to a passive orthostatic challenge in elderly fallers (black) vs non-fallers (white) (Shaw et al., 2015, p. 5 of 8).



1.2.5 Summary

- The prevalence of CKD-5 has increased over the last 10 years in the UK, as the numbers of patients requiring RRT has grown by 39% compared to 2006 (UKRR, 2016). HD therapy is the most common modality of RRT in the UK (41% of CKD-5 patients are maintained on HD), and it is also the most expensive, with a yearly estimated cost per patient of over £35K (Baboolal et al., 2008).

- The median age of HD patients has increased over the last 10 years, and is now 67 years (UKRR, 2016). Consequently, adverse outcomes which are typical of the geriatric population, such as falls and falls-related injuries, are also expected to rise in this population, and are going to raise the economic burden for the NHS, due to the medical expenses required to treat the fall-related injuries.

- The WHO global report on the prevention of falls in older age (2008) characterised the economic burden of falls in terms of direct costs, such as the expenses for the health care systems relative to the medications and services for the treatment and rehabilitation of injuries arising from falls, and indirect costs, such as the possible productivity loss of family caregivers. NHS data (2008) suggests that, over the next 20 years, the estimated increase in direct costs from falls would amount to £200 million in the UK.

- Prospective cohort studies with a 12-month observational follow-up suggest that 26.3% to 55% of HD patients experience at least one fall every year (Abdel-Rahman et al., 2011; Polinder-Bos et al., 2014), with an incidence of falls ranging from 0.38 to 1.6 falls/patient-year (Abdel-Rahman et al., 2011; Cook et al., 2006). These reports are generally indicative of an increased risk of falling in CKD-5 patients on HD compared to the general, non-uraemic, population of community-dwelling older adults (WHO, 2008). However, no data from 12-month prospective studies of the incidence of falls in HD patients are currently available in the UK.

- A number of observational studies described various risk factors associated with the occurrence of falls in CKD-5 patients on dialysis, with older age, previous history of falls, polypharmacy, depression and/or antidepressants use, comorbidities, frailty, and low blood pressure with or without symptomatology the most commonly reported. Frailty and blood pressure dysregulation are two risk factors that may be, at least partly, exercise-modifiable.

- A recent systematic review with meta-analysis suggests that the prevalence of frailty in CKD-5 patients is 36.8%, which is approximately 5 times higher than in the healthy elderly population (Kojima et al., 2017). Although an increasing number of studies strongly support the hypothesis that frailty is associated with a higher occurrence of falls and fall-related injuries in CKD-5 patients on HD (McAdams-DeMarco et al., 2013; Kutner et al., 2014; Delgado et al., 2015), the relationship between the single frailty domains of low physical function/activity, which are potentially exercise-modifiable, and falls warrants further investigation. Approximately half of the studies investigating falls behaviour in CKD-5 patients did not include physical function/activity assessments at all as potential risk factors of falls, or only included self-reported measurements of physical function/activity, which are generally considered less reliable than objective measurements. The other half of the studies reported contrasting results, as only a few studies found a significant association between objective measurements of physical function and falls among dialysis patients, while others did not highlight any significant association. Further research aimed to identify which prevalent risk factors may be more closely associated with falls in CKD-5 patients on HD, is of paramount importance, as this would eventually allow to tailor interventions aimed to reduce the occurrence of falls in these patients.

- Along with frailty, CVD is a common feature of CKD-5 patients and represents the lead cause of mortality in these patients. Autonomic dysfunction is one of the main mechanism that can lead to CVD, and as some research has suggested, it could also

be implicated in the clinical manifestation of dizziness, syncope-like events and possibly falls in HD patients (Roberts et al., 2003). Baroreflex function is one of the most common assessment, in the context of autonomic function testing, and it has been consistently shown to be impaired in CKD-5 patients (Rubinger et al., 2013; Hildreth et al., 2012). The deterioration of baroreflex function may be one of the main mechanisms to negatively affect the regulation of blood pressure in resting conditions, but also in the upright position or during the transition from a seated/supine position to upright standing because it is the main physiologic mechanism that controls the cardiovascular responses to short-lived changes in body position or during exercise. Despite the overwhelming evidence that baroreflex function is impaired in CKD-5 patients, along with the observations that HD patients often present with dizziness, low blood pressure spells, and that around 33% of falls occur during the transition from a lying down or seated position to upright standing (Cook et al., 2006), no research has explored the relationship between the baroreflex, the cardiovascular responses to orthostasis, and falls in CKD-5 patients on HD yet. Because baroreflex function is a potentially exercise-modifiable factor (Petraki et al., 2008), rehabilitation programs aimed to restore baroreflex function could be developed and implemented in the context of falls prevention in HD patients.

1.2.6 Research questions

Question 1:

Are CKD-5 patients on HD at high risk of falling? (Chapter 3)

Hypothesis:

The prevalence of HD patients experiencing at least one fall over 12 months, as well as the incidence of falls, will be indicative of an increased risk of falling compared to the estimates of falls from the non-uraemic population;

Question 2:

Are frailty and its physical function/activity components associated with falling in CKD-5 patients on HD? (Chapter 4)

Hypothesis:

The Fried's frailty phenotype, and objective measurements of physical function/activity will be associated with the falling status in HD patients;

Question 3:

Are the cardiovascular responses to orthostasis associated with falling in CKD-5 patients on HD? (Chapter 5)

Hypothesis:

Baroreflex function, and the haemodynamic responses to a passive orthostatic challenge will be associated with the falling status in CKD-5 patients on HD;

Question 4:

What is the relative importance of frailty and cardiovascular function as potential exercise-modifiable risk factors for falls in CKD-5 patients on HD? (Chapter 6)

Hypothesis:

Modelling the risk of falling by adding an exercise-modifiable cardiovascular function variable to a frailty-related variable only will improve the prediction of the number of falls sustained over a 12-month period in CKD-5 patients on HD.

CHAPTER 2: GENERAL METHODS

2.1 Recruitment

2.1.1 Ethical approval

This research project was carried out according to the ethical principles for medical research involving human subjects as set out by the world medical association declaration of Helsinki. The Research Ethics Committee at Queen Margaret University, and the West of Scotland REC 3 reviewed and approved the research project (NHS REC reference number: 15/WS/0079; Appendix I). Research and Development approval at Monklands Hospital, NHS Lanarkshire, and at Victoria Hospital, Kirkcaldy, NHS Fife were also obtained (Appendices II and III).

All patients undergoing outpatient HD therapy at Monklands Hospital and Victoria Hospital were firstly screened for eligibility by a member of the renal team responsible for their care, and if they registered a preliminary interest for the study, they were provided with a participant information sheet (PIS) detailing all the procedures involved with this research (Appendix IV). All patients were given at least seven days to consider the information and make a decision and/or enquire further about the study. After this period, the researcher approached potential participants and gained written informed consent (Appendix V) from all the patients agreeing to take part in the research project.

2.1.2 Participants

A convenience sample of ambulatory CKD-5 patients meeting the following eligibility criteria i) men and women ii) undergoing HD therapy (for at least 3 months) thrice weekly iii) older than 18 years iv) able to understand and speak English were recruited from two dialysis units at Monklands Hospital, Airdrie, NHS Lanarkshire, and Victoria Hospital, Kirkcaldy, NHS Fife.

Exclusion criteria applied were: i) unstable dialysis and medication treatment as defined by renal care team, ii) lower limb amputees without prosthesis, iii) unstable cardiac condition, iv) suspected or known aneurysm, v) clinically severe left ventricular outflow

obstruction, vi) critical mitral stenosis, vii) critical proximal coronary artery stenosis, viii) critical cerebrovascular stenosis, ix) pregnancy, and x) severe cognitive impairment.

2.1.3 Sample size

In order to establish the association of risk factors with falling status, a logistic regression modelling approach was adopted. In logistic regression analysis, Peduzzi et al. (1996) recommended a ratio of 10 events per explanatory (independent) variable by the smaller proportion of the binary dependent variable, to allow unbiased estimation of associations. For the purposes of this research project, the number of events was defined as the number of people who experienced at least one fall over an observation period of 12 months (assuming prevalence of falls ≤ 50%). Background literature suggests that between 26% and 47% of patients on HD experience at least one fall over a period of 12 months (Cook et al., 2006, Abdel-Rahman et al., 2011). Hence, by using the smallest prevalence of falls reported (26%), a sample of 100 participants will have 26 fallers (events) and, using Peduzzi's rule (10 events per explanatory variable), would allow 2 or 3 (2.6) variables to be entered in the same regression model. Assuming a prevalence of falls equal to 47% however, the logistic regression model would allow inclusion of 4 or 5 ('4.7') independent variables for a sample size of 100.

In order to answer PhD research questions 2, 3 and 4 (Chapter 1, paragraph 1.2.6), at least two or three explanatory variables would be required. This would be achieved by modelling the risk of falling using one measure of frailty (e.g. gait speed), one measure of cardiovascular function (e.g. baroreceptor effectiveness index) and/or adjusting for clinical confounders. Table 2.1 further illustrates how many participants would be required for a given number of predictor variables depending on different prevalence of falls over a range of observation periods.

Table 2.1. A priori estimation of sample size (n).

		Prevalence of falls			
		12.7% (*Desmet et al. 2005, over 8 weeks*)	**38%** (*Roberts et al. 2007, over 6 months*)	**26%** (*Abdel-Rahman et al. 2011, over 12 months*)	**47%** (*Cook et al. 2006, over 12 months*)
Number of covariates	**2**	n= 157	n= 53	n= 77	n= 43
	4	n= 315	n= 105	n= 154	n= 85
	6	n= 472	n= 158	n= 231	n= 128
	8	n= 630	n= 211	n= 308	n= 170
	10	n= 787	n= 263	n= 385	n= 213

2.1.4 Data protection and confidentiality

All data from questionnaires and physical tests were collected in accordance with the terms of the Data Protection Act (1988), the General Data Protection Regulation (2018), and met the criteria of the NHS Lanarkshire, and NHS Fife confidentiality policies. All data were treated confidentially and reported anonymously.

Each participant was allocated a unique identifier code and was identified by this and not his/her name. Electronic data were stored on a secure NHS password protected laptop and paper data were stored in a locked filing cabinet at Queen Margaret University. Data downloaded onto the Task Force® Monitor PC and ActivPal™ chip were removed once this information was transferred onto the secure laptop. Anonymised data were analysed at Queen Margaret University. At this stage, any information collected had the participants' names removed or coded so that they could not be identified at any time during data analysis. Electronic data for analyses purposes were transported from the hospitals to Queen Margaret University via an encrypted memory stick or password protected laptop.

2.2 Assessment of frailty

2.2.1 Fried's frailty phenotype

The assessment of frailty was based on the work of Fried and colleagues (2001) who defined frailty as a biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes. Fried characterised this syndrome in terms of a frailty phenotype consisting of five components: shrinkage, low levels of PA, poor strength, low gait speed, and self-reported exhaustion. These components are operationalised as described below (Fried et al., 2001): subjects meeting at least 3 out of these 5 criteria are classified as frail.

1. Shrinkage: Unintentional weight loss of at least 10 pounds (4.5 kg) in the previous 12 months.
2. Low levels of PA: This variable is derived from the Minnesota Leisure Time Activity questionnaire, and is stratified by gender. Men reporting < 383 Kcal of PA per week, and women reporting < 270 Kcal of PA per week are classified as frail;
3. Poor strength: This variable is based on handgrip scores and is stratified by gender and BMI quartiles. Men and women with handgrip scores lower than the cut-off values listed below are classified as frail:

Men, BMI ≤ 24	Handgrip (kg) ≤ 29
Men, BMI 24.1 – 26	Handgrip (kg) ≤ 30
Men, BMI 26.1 – 28	Handgrip (kg) ≤ 30
Men, BMI > 28	Handgrip (kg) ≤ 32
Women, BMI ≤ 23	Handgrip (kg) ≤ 17
Women, BMI 23.1 - 26	Handgrip (kg) ≤ 17.3
Women, BMI 26.1 - 29	Handgrip (kg) ≤ 18
Women, BMI > 29	Handgrip (kg) ≤ 21

4. Low gait speed: This variable is based on the time spent to walk a 15 feet (4.57 m) distance, and is stratified by gender and height. Men and women

scoring times lower than the cut-off values listed below are classified as frail:

Men, height ≤ 173 cm	Time (s) ≥ 7
Men, height > 173 cm	Time (s) ≥ 6
Women, height ≤ 159 cm	Time (s) ≥ 7
Women, height > 159 cm	Time (s) ≥ 6

5. Self-reported exhaustion: This variable is assessed by means of the CES-D Depression Scale. The statements "I felt that everything I did was an effort", and "I could not get going" are read and the following question is asked "How often in the last week did you feel this way?". Four answer options are given: 0 = rarely or none of the time; 1 = some or a little of the time; 2 = a moderate amount of the time; 3 = most of the time. People answering "2" or "3" are classified as frail.

2.2.2 Classification of frailty status

Participants were classified as frail and non-frail based on an adaptation of the Fried's frailty phenotype described above. Patients scoring at least 3 out of the 5 following criteria were classified as frail:

1. Shrinkage: Unintentional weight loss of at least 10 pounds (4.5 kg) in the previous 12 months from the date of assessment. This information was retrieved from the renal unit electronic patient record system (SERPR);
2. Low levels of PA: This frailty component was derived from the Short IPAQ questionnaire, and was stratified by gender. Men reporting < 383 Kcal of total PA per week, and women reporting < 270 Kcal of total PA per week were classified as frail (Fried et al., 2001);
3. Poor strength: This component of frailty was based on the handgrip scores, stratified by gender and BMI quartiles, as described by Fried et al., (2001). Men and women with handgrip scores lower than the cut-off values listed below were classified as frail:

Men, BMI ≤ 24	Handgrip (kg) ≤ 29
Men, BMI 24.1 – 26	Handgrip (kg) ≤ 30
Men, BMI 26.1 – 28	Handgrip (kg) ≤ 30
Men, BMI > 28	Handgrip (kg) ≤ 32
Women, BMI ≤ 23	Handgrip (kg) ≤ 17
Women, BMI 23.1 - 26	Handgrip (kg) ≤ 17.3
Women, BMI 26.1 - 29	Handgrip (kg) ≤ 18
Women, BMI > 29	Handgrip (kg) ≤ 21

4. Low gait speed: This component was also based on the time spent to walk a 15 feet (4.57 m) distance, stratified by gender and height, as described in the frailty phenotype (Fried et al., 2001). Men and women scoring times lower than the cut-off values listed below are classified as frail

Men, height ≤ 173 cm	Time (s) ≥ 7
Men, height > 173 cm	Time (s) ≥ 6
Women, height ≤ 159 cm	Time (s) ≥ 7
Women, height > 159 cm	Time (s) ≥ 6

5. Self-reported exhaustion: The exhaustion component was assessed by means of the vitality scale of the SF-36 questionnaire. Participants with a score < 55 were classified as frail

Two components of the frailty phenotype, namely the low PA and self-reported exhaustion, were measured with different tools with respect to the work of Fried and colleagues (2001). The Short-IPAQ was used instead of the Minnesota Leisure Time Activity questionnaire, as the IPAQ has been used more consistently in CKD patients (Li et al., 2010; Rosa et al., 2015; Nah et al., 2019).

Also, the SF-36 questionnaire was preferred to the CES-D depression scale for the assessment of the self-reported exhaustion component of frailty. The vitality scale of the SF-36 has become a commonly used tool in assessing this frailty component in dialysis populations: a score < 55 on the vitality component of the questionnaire has been used by previous literature as a measure of self-reported exhaustion, when assessing the

prevalence of frailty in patients undergoing haemodialysis therapy (Johansen et al., 2007; Delgado et al., 2013).

It should be noted that, although the Fried's phenotype was developed from a population of U.S. older adults living in the community, adaptations of this frailty phenotype have also been widely used in large UK population-based studies (Hanlon et al., 2018; Kojima et al., 2019; Watts et al., 2019). In the operational definition of frailty given by Fried et al., (2001), the cut-off values of the objectively recorded components "grip strength" and "gait speed" were obtained from the lowest quintile of distribution in the study participants (adjusted for gender and BMI/height). Consequently, UK studies conducted in older populations have often derived the cut-off values of these two components based on the distribution of the grip strength and gait speed scores (lowest quintile) in the actual study population (Watts et al., 2019) rather than using the cut-off values presented in the study by Fried. Although this is a sensible strategy to account for inter-country differences, our study population (CKD-5 patients on HD) is not comparable with the general population of community-dwelling older adults. Therefore, we felt that deriving the cut-off values from the lowest quintile of distribution would not reflect an accurate estimation of weakness and slowness prevalence in the research participants.

2.3 Physical function measurements

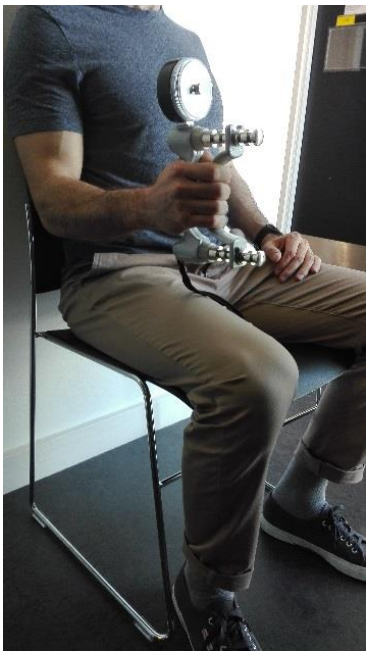
2.3.1 Handgrip strength

All participants underwent handgrip strength testing using the Jamar hand dynamometer (Lafayette Instrument Company®, USA). This instrument has shown the best inter-rater and intra-rater reliability in clinical and epidemiological studies, and is commonly referred to as the gold standard for the assessment of handgrip strength (Roberts et al., 2011).

Before starting the test, the dynamometer handle was adjusted to accommodate the palm's size of every participant (Koufaki and Kouidi, 2010). For the assessment (Figure 2.1), participants sat on a chair, with the elbow of the testing arm flexed at 90 degrees, and the forearm in the neutral position (Roberts et al., 2011). The execution of this test was demonstrated beforehand and patients had the chance to familiarize themselves with the procedure once or twice. The following standardized verbal instructions were given: "Sit

back with your elbow flexed at 90 degrees and your forearm in the neutral position. I will count backwards 3… 2… 1… GO. When I say GO, please squeeze the handle as hard as you can for five seconds. Remember to breathe out during the test, and don't hold your breath". Also, standardized verbal encouragement was provided throughout the assessment: "Harder! Harder! Relax" (Mathiowetz et al., 1984). Three measurements rounded to the nearest kg were recorded and the average of these measurements was used for data analysis. After each measurement the peak-hold needle of the dynamometer was reset to zero and a 60 seconds recovery time was allowed between one measurement and the next. The three measurements were taken from the dominant hand, which in most cases corresponded to the limb free from fistulas. Measurements from the fistula arm were also allowed granted that this was well healed (Koufaki and Kouidi, 2010).

Figure 2.1. Handgrip strength: standardised grip position.



2.3.2 Isometric leg extension maximal voluntary contraction

The apparatus for the assessment of isometric leg (knee) extension maximal voluntary contraction (MVC) consisted of a 45 cm (height) - 50 cm (width) - 40 cm (depth) chair, a goniometer, and a digital myometer (MIE, Medical Research Ltd, Leeds, UK). This

apparatus has been used to evaluate the effects of an exercise intervention in renal patients (Greenwood et al., 2015), and although the validity-reliability characteristics of the digital myometer are not available for the renal population, it has been shown to have good intra-rater and inter-rater reliability in children with cerebral palsy (Thompson et al., 2011), and in stroke patients (Bale et al., 2008).

The participants were asked to sit upright on the chair (90° of trunk flexion), with their hands crossed across the chest (Figure 2.2), and with an angle of 80° of knee flexion (full knee extension= 0°), which is considered an optimal angle for knee extension torque (Aagaard et al., 2000). The terminal part of the dynamometer was strapped to the ankle joint just above the malleoli, and the angle at the knee was measured with a goniometer while making sure that the strap applied to the ankle was pre-tensioned before commencing the test. The task was demonstrated by the researcher and the participants practiced once or twice, before commencing the test following these instructions: "I would like you to sit upright on this chair and to cross your hands on the shoulders. I will say: 3… 2… 1… GO. When I say go, please push as strong and as fast as you can, as if you were to extend your leg, until I tell you to stop".

The force produced in kg was recorded from three measurements from the dominant limb. If participants were unsure about which leg to use, they were asked to think about which leg they would use to kick a ball, and to use that limb for the assessment. The average of the three following measurements was used for data analysis. After every measurement, the dynamometer screen was reset to zero, the knee angle was measured again from the pre-tensioning position, and a 60 seconds interval was allowed before the following measurement.

Figure 2.2. Isometric leg extension MVC: standardised assessment position.

2.3.3 Postural balance

An assessment of postural static balance was performed by means of a Bertec® BP5050 (Bertec Corporation, Columbus, Ohio, USA) force platform, which has been previously used to assess fall-risk in elderly people living in the community (Bigelow et al., 2011). The assessment protocol consisted of standing as still as possible for 30 seconds on the force platform under two different conditions: eyes open and eyes closed. The platform was placed distant from walls or other objects that could be used as a support during the measurement. For safety reasons, the researcher was standing close to the participant during the assessment in case he/she suffered a sudden loss of balance. In addition, a focal point for participants to stare at during the assessment was placed 3 metres in front of the platform. Participants were instructed how to position their feet on the platform before starting the measurements. A 30° angle with heels slightly apart (3-5cm) orientation (Figure 2.3) was chosen as this was judged to be more suitable than a position with the longitudinal axes of the feet parallel to each other for participants with poor physical function and balance (Scoppa et al., 2017). The 30° angle was marked on the platform by using adhesive tape to guide the participants on the required position of their feet. An

additional piece of tape was placed on the platform to mark the position on which the heels should be aligned. The correct feet positioning was demonstrated prior to commencing the assessment by the researcher and the following verbal instructions were given: “This assessment consists of standing upright on the force platform as still as possible, with your arms relaxed along the body sides. Please stare at the focal point that is located just in front of you for the whole duration of the assessment. Make sure you place your feet on the lines marked by the adhesive stripes, and that you align your heels on the posterior line. The measurement will start when I say “START” so please try to stay as still as possible from then onwards. I will prompt you when you can move again”. The balance assessment was performed in eyes open (EO) and eyes closed (EC) conditions: every testing condition was performed twice, and data were recorded for 30 seconds, which is recommended in order to achieve acceptable test retest reliability (Le Clair et al., 1996).
Centre of pressure (COP) data for the anterior-posterior (AP) and medial-lateral (ML) sway directions were collected at 1000Hz. The following COP measures were subsequently computed from the raw COP data (XY components) using custom written MATLAB (Mathworks®, USA) scripts over the 30s period: range of COP displacement along the ML (RangeX) and AP (RangeY) axis, root mean square displacement along the ML (RMSX) and AP (RMSY) axis, total sway path (SP), mean absolute velocity (AbsVel), mean velocity along the ML (VelX), and AP (VelY) axis, and the 95% confidence ellipse area (Area95). Finally, the average of the two measurements was calculated for every variable and was taken for data analysis purposes.

Figure 2.3. Postural balance: apparatus and standardised assessment position.

2.3.4 Gait speed

A simple gait speed test was performed on a flat, anti-slip surfaced hospital corridor. The test consisted of the 15 feet walk test used by Fried's and colleague as a measure of the frailty phenotype (Fried's et al., 2001). The extremities of the 15 feet track (4.57 meters) were marked with adhesive tape, and a stopwatch was used to record the time. The participants were encouraged to walk with a self-selected speed, reflecting their normal walking pace habits. The following instructions were given: "I will say 3… 2… 1… GO. When I say go, please walk from this mark on the floor up to the second mark on the floor in front of you". Participants were allowed to use their normal assistive walking devices (e.g. cane) if necessary. Participants performed two trials interspersed by a 30 seconds interval, and the two measurements were averaged for data analysis purposes.

2.3.5 Timed Up and Go

A Timed Up and Go (TUG) test was performed in a corridor of the hospitals designated for the physical function tests. This test was executed along a 3 meters track: a line on the floor was marked with coloured adhesive tape 3 meters in front of the chair (45 cm (height)

- 50 cm (width) - 40 cm (depth)) that was used for the assessment (Figure 2.4). A digital stopwatch was used to record the time.

The TUG assesses dynamic balance by asking the individual to stand up from a chair, walk 3m, turn, walk back to the chair and sit down again, as quickly as possible (Podsiadlo et al., 1991). TUG performance is a sensitive measure for identifying individuals at increased risk of falls, particularly a time ≥ 14 seconds has been shown to discriminate fallers versus non fallers in older but otherwise healthy adults (Shumway-Cook et al., 2000), and it can be improved with physical exercise in patients undergoing maintenance HD therapy (Greenwood et al., 2012).

Before commencing the test, the researcher demonstrated the TUG procedure to the participants, and inspected the floor to make sure it was free from slip or trip hazards. The following verbal instructions were provided: "Please sit upright with your back against the seatback, rest your hands on your knees, and make sure both your feet are touching the ground. I will say: 3… 2… 1… GO. When I say go, please stand up from the chair, walk until the mark on the floor, turn back making sure you walk around this mark, and go and sit back on the chair. Walk at walking speed you find comfortable but do not run. Timing will start when I say GO, and will finish when you sit down on the chair again." Participants were allowed to use their normal walking aids if required, and the researcher took a note if this was the case (Schumway-Cook et al., 2000). The test was executed twice as performing two trials of the TUG has been suggested to increase the reliability of this test in chronic renal failure patients (Mesquita et al., 2013). Up to 60 seconds rest between the two measurements was allowed to reduce any possible fatigue effects. The average of the two trials was taken for the data analysis.

Figure 2.4. TUG: standardised procedure.

2.3.6 Chair sit to stand five test

A Chair sit to stand five (CSTS-5) test was performed using a standard 45 cm (height) - 50 cm (width) - 40 cm (depth) chair, and a digital stopwatch.

The CSTS-5 reflects lower limb muscle power generation capacity by measuring the time it takes for an individual to rise from a chair repeatedly 5 times, as quickly as possible (Guralnik et al., 1994). Low performance in this functional test (time to rise from the chair ≥16.7 seconds) has recently been associated with an increased risk of injurious falls in older adults (Ward et al., 2015). In addition, this physical function test has been shown to have good concurrent validity and to discriminate people with and without balance deficits (Whitney et al., 2005). The researcher explained and demonstrated the task to the participant beforehand. The chair was placed against a wall to prevent any movement during the assessment (Figure 2.5). The following verbal instructions were given prior to starting the assessment: “Please sit upright in the middle of the chair, keeping your hands crossed at shoulder level, and make sure both of your feet are touching the ground. I will say: 3… 2… 1… GO. When I say go, you will rise from the chair for 5 consecutive times as quickly as possible. It is very important that you achieve a full extension of your knees

and trunk and that you don't lift your feet from the ground when sitting back on the chair. Also, don't sit completely back on the chair when you sit down, but rather you should try to stand up again as soon as your buttocks touch the chair. Timing will start when I say GO, and will finish when you sit down on the chair after the fifth repetition". Participants' understanding of the procedure was checked by asking them to repeat the instructions given to them. Participants unable to rise from the chair independently were excluded from this assessment, or alternatively they executed the test by keeping the hands on their knees during the measurement. The researcher took a note of whether the person could perform the assessment as per instructions given, or whether he/she was unable/required assistance. One recording rounded to the hundredth of a second was taken for the data analysis.

Figure 2.5. CSTS-5: standardised procedure.

2.3.7 SF-36™ Health Survey

The UK Standard English (Version 2) SF-36™ Health Survey was completed by all participants as a measure of perceived quality of life (Appendix VI).

The SF-36™ Health Survey is a multi-item scale measuring 8 health concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health (Ware et al., 1993). The SF-36™ questionnaire has been used extensively to assess health-related quality of life in patients undergoing HD therapy, including the dialysis outcomes and practice patterns study (DOPPS) (Mapes et al., 2004), and is a strong predictor of hospitalization and mortality (Lowrie et al., 2003). The questionnaire has good psychometric properties with high reliability and construct validity (Korevaar et al., 2002). Participants completed this self-administered questionnaire at the start of their assessment visit. Instructions for the completion of the SF-36™ were available on the front pages of the questionnaire, and the researcher also rendered himself available for further clarifications in case of any possible doubts. The questionnaire was administered by the researcher if the participant had a significant visual impairment. The raw scores from the completed questionnaires were entered onto an SPSS spreadsheet and an appropriate SPSS syntax, depending on sex (males syntax or females syntax) was used to transform the raw scores in aggregated scores (0-100 range) for the 8 health domains. The physical component summary score (PCS) and mental component summary score (MCS) were also computed by means of SPPS syntaxes.

2.4 Assessment of physical activity levels

2.4.1 ActivPal™ monitor

The ActivPal™ physical activity monitor (PAL technologies Ltd, Glasgow) was used to objectively record habitual physical activity (PA).

This device is a uniaxial accelerometer that measures time spent standing, sitting/lying and, stepping and the pace of stepping. It also records the number of steps and the number of sit-to-stand and stand-to-sit transitions. This information is captured by a piezoresistive accelerometer that detects posture changes and movement from inclination of the thigh.

The ActivPal™ monitor software utilizes algorithms to convert the information coming from the inclination of the thigh in the outcomes of interest. The monitor has been shown to be valid and reliable in discerning sedentary and upright activities, and in recognizing body transitions from sitting and lying positions to the upright standing position (Taraldsen et al., 2011). In addition, the ActivPal™ has been shown to have good concurrent validity and reliability in assessing the number of steps taken in healthy adults (Ryan et al., 2006) and in inpatients admitted to a rehabilitation unit (Treacy et al., 2017). More recently, it has been suggested that this PA monitor is a valid tool in discerning activity intensity levels in healthy adults (Lyden et al., 2017). Data are captured at a frequency of 10 Hz, and the monitor is able to record data for more than 8 days continuously.

2.4.1.1 Wear protocol

Participants were given standardised written instructions on how to use and position the ActivPal™ monitor correctly by means of a leaflet (Appendix VII), and the researcher also explained all the procedures on the assessment day, when the monitor was attached to their thigh. The device was worn on the anterior aspect of the thigh as per manual instructions: on the front mid-line of the thigh a third of the way between the hip and knee (Figure 2.6). PALstickies™ and hypoallergenic adhesive tape were used to keep the monitor in place during data acquisition.

Participants were asked to remove the monitor prior to showering or taking a bath, and were also allowed to take it off at night time for their own comfort if they wished. In addition, they were provided with a physical activity diary to be filled out daily: they were instructed to take a note of the exact times the monitor was worn throughout the day, and also the time they removed it for any reasons. Participants were required to wear the ActivPal™ monitor for at least five consecutive days, starting from the day of the assessment. The monitor was collected from the participant, at the end of the recording period, during a routine HD session at Monklands Hospital, or at Victoria Hospital. The data were downloaded onto a PC and processed using the ActivPal™ software (Version 6.4.1).

2.4.1.2 Data cleaning and outcomes

The first day of ActivPal™ monitor wearing was discarded from the data analysis, because it was considered a practice day. The minimum wearing time required for the data to be included in the final analysis was at least three days consisting of two non HD days and one HD day, with at least 8 hours of daily wearing (Prescott et al., 2014). Participants not achieving this duration were removed from the data analysis. The ActivPal™ software was used to double check the minimum required wearing time, as well as to convert the raw accelerometry data to the outcomes of interest, namely time spent standing, time spent stepping, number of sit to stands, and number of steps taken. An Excel spreadsheet summarising the daily and weekly breakdown of the various outcome measures was generated from the ActivPal™ software, and the 24 hours averages of each variable were calculated and used for data analysis.

Figure 2.6. ActivPal monitor: standardised positioning.

2.4.2 International physical activity questionnaire short format

Participants completed the International physical activity questionnaire (IPAQ) short format during the assessment day as a subjective measure of PA (Appendix VIII).

The Short IPAQ is a self-administered 4-item questionnaire on the participants' physical activity levels during the last 7 days, and has been demonstrated to have good validity and reliability (Craig et al., 2003). Three of these items assess the frequency and duration of the following types of activities: walking, moderate-intensity activities, and vigorous-intensity activities. The fourth item assesses sedentary behaviour by asking how many hours the person spends sitting on a daily basis. The raw scores of frequency and duration, expressed in days and minutes respectively, were entered onto an Excel spread sheet and they were transformed to MET-minutes/week and Kcal/week by using a physical activity compendium (Ainsworth et al., 2000) as described in the guidelines for data processing and analysis of the IPAQ. The following formulae were used

- Walking MET-minutes/week = 3.3* walking minutes * walking days;
- Moderate MET-minutes/week = 4.0* moderate-intensity activity minutes * moderate-intensity activity days;
- Vigorous MET-minutes/week = 8.0* vigorous-intensity activity minutes * vigorous-intensity activity days;
- Total PA MET-minutes/week = sum of walking + moderate + vigorous MET-minutes/week scores.
- Walking Kcal/week = (3.3* walking minutes * walking days)*(body mass/60);
- Moderate Kcal/week = (4.0* moderate-intensity activity minutes * moderate-intensity activity days)*(body mass/60);
- Vigorous Kcal/week = (8.0* vigorous-intensity activity minutes * vigorous-intensity activity days)*(body mass/60);
- Total Kcal/week = sum of walking + moderate + vigorous Kcal/week scores.

A categorical score of PA was also obtained from the IPAQ scoring guidelines. Participants were classified as high, moderate, or low self-reported levels of PA following the guidelines' recommendations:

- High PA = participants meeting either of these 2 criteria:

a) At least 3 days of vigorous-intensity activity achieving a Total PA of at least 1500 MET-minutes/week;
b) Total PA of at least 3000 MET-minutes/week deriving from 7 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities;

- Moderate PA = participants meeting any of the following criteria:
    a) At least 20 minutes per day of vigorous-intensity activity on 3 or more days;
    b) At least 30 minutes per day of walking and/or moderate-intensity activity on 5 or more days;
    c) Total PA of at least 600 MET-minutes/week deriving from 5 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities;
- Low PA = participants not meeting any of the criteria described above.

The IPAQ has been previously used in patients undergoing HD (range of age: 18-86 years old), and its scores have been positively associated with physical function, as assessed by the SF-36 Health Survey, in this clinical population (Li et al., 2010).

2.5 Assessment of baroreflex and haemodynamic function

2.5.1 Head up tilt test: introduction

In 1986, the head up tilt (HUT) test was first reported to represent a useful procedure to investigate episodes of syncope (Kenny et al., 1986), namely an event characterised by transient loss of consciousness as a result of sudden cerebral hypoperfusion arising (typically) from low blood pressure (BP) (Brignole et al., 2004). In that study, the authors described an abnormal response of systolic blood pressure and heart rate in patients with history of unexplained syncope after 60 minutes of HUT at 40°. Ten years later, the HUT test was appointed as the gold standard for the clinical evaluation of patients presenting with syncope-related symptoms by an expert consensus document (Benditt et al., 1996), and the combined use of HUT and non-invasive measurements of BP, heart rate (HR), and

other haemodynamic parameters have become routinely integrated in clinical practice for the diagnosis of syncopal events.

Given the relatively recent implementation of the HUT test in clinical practice, several approaches, with regard to the assessment protocol, are available and the most common strategies relating to the testing procedure aspects are synthesized below:

Tilt angle

The first work of Kenny et al., (1986) proposed a tilting angle of 40° over 60 minutes of HUT. Since this first publication, the effect of various protocols adopting different tilt angles on the haemodynamic responses and onset of syncope have been described in the literature: a range of tilt angles between 20° and 90° has been investigated (Khurana et al., 1996). A study by Fitzpatrick et al., (1991) showed that using a tilt angle of 45° resulted in a significant lower rate of positive responses (syncopal events) compared to a 60° angle, and lower specificity for tilt angles <60° was also reported by Kapoor et al., (1994). At the same time, tilt angles between 60° and 90° don't seem to differ substantially in terms of the predictive ability of the test (Khurana et al., 1996), therefore 60° became the threshold tilt angle for the diagnosis of syncopal events. Tilt angles between 60°-80° are widely accepted in clinical practice, whereas the 60°-70° range is the most commonly used (Benditt et al., 1996).

Another common recommendation, regarding the tilt angle, is that the table should be designed to achieve the desired angle as smoothly as possible and in a relatively rapid time (10-15 seconds). The tilt-down should also be achieved as rapidly as possible in case of positive response to the HUT test, or if any signs lead the medical team to wish interrupting the assessment (Benditt et al., 1996).

Tilt duration

Another crucial aspect of the HUT test, even more important than the tilt angle, is the duration of the tilting phase. Research protocols with tilting durations between 2 and 60 minutes have been described in the literature (Khurana et al., 1996).

Despite the great heterogeneity, the recommendation for the tilt duration is of at least 30-45 minutes, if the purpose of the HUT test is that of diagnosing syncope (Benditt et al., 1996), as the onset of syncope at 60° occurs on average after 22-24 minutes of HUT (Fitzpatrick et al., 1991; Kapoor et al., 1994). The duration of the tilting phase also depends on whether or not vasodilator drugs are administered during the assessment: a shortened protocol consisting of 20 minutes of HUT at 60° followed by sublingual administration of nitroglycerin was shown to have similar specificity to a more time demanding HUT protocol (Del Rosso et al., 2000).

Drug challenge

Although the HUT test was first introduced as a drug-free assessment (Kenny et al., 1986), some research explored the effects of combing drugs that could potentially facilitate the occurrence of syncopal events with HUT, in order to improve the predictive ability of this kind of assessment. Particularly, the infusion of isoproterenol (Almquist et al., 1989) and sublingual administration of nitroglycerin (Raviele et al., 1995) were shown to be useful tools in diagnosing neurally mediated syncope, and their use became widely popular in clinical practice since then.

2.5.1.1 Testing protocol: premise

For the purposes of this PhD project, a HUT test with relatively short tilting duration (five minutes) was employed. This choice was based on the current guidelines on the management of syncope which define orthostatic hypotension as a fall in systolic BP (SBP) ≥20mmHg and diastolic BP (DBP) ≥10mmHg within the first 3 minutes of standing up from a supine position or during HUT at 60° (Brignole et al., 2004).

In healthy individuals, the transition from supine position to upright standing results into a gravitational shift and pooling of 300-800 ml of blood to the lower extremities and the venous capacitance system within the first 10 seconds (Freeman et al., 2011). This mechanical gravitational pooling of blood volume in the lower extremities triggers a series of integrated physiological events and adjustments that all ultimately aim to maintain adequate pressure in the cardiovascular system as indicated by mean arterial pressure

(MAP). In brief, gravitational pooling of blood volume results in a decreased venous return to the heart, and subsequent reduced cardiac filling, which leads to decreased stroke volume and cardiac output and thus drop in MAP. The autonomic nervous system prevents hypotension by increasing the sympathetic outflow which stabilizes BP through increased vascular tone, cardiac contractility and HR. The component of the autonomic nervous system that is mainly responsible for these short-term inotropic (vasoconstriction) and chronotropic (HR increase) responses is the arterial baroreceptor reflex, while other mechanisms like the renin-angiotensin-aldosterone system are involved during prolonged standing (Freeman et al., 2011).

Therefore, the purpose of the HUT protocol used in this PhD research project was to identify the possible inadequate short term reflex mechanisms that could lead to orthostatic hypotension and associated symptoms such as dizziness and possibly falls (Roberts et al., 2003), by assessing the short-term regulation of BP and other haemodynamic responses, including the baroreceptor reflex activity, rather than diagnosing syncope which would require a longer tilting duration, a procedure that could be less well tolerated by patients on HD (Benditt et al., 1996).

2.5.1.2 Testing protocol: HUT-60°

Participants underwent a 60° HUT test (HUT-60°) to assess the short-lived baroreceptor reflex and haemodynamic responses to a passive orthostatic challenge.

The Task Force® Monitor 3040i (CNS systems, Graz, Austria) was used to record the BP and HR responses continuously throughout the assessment. This device allows the simultaneous measurement of HR, BP, and other haemodynamic variables (total peripheral resistance, stroke volume, cardiac output, heart rate and blood pressure variability) by means of 6-lead electrocardiography (ECG), continuous photoelectric plethysmography, and impedance cardiography (ICG). Oscillometric blood pressure (oscBP) was also measured with an electronically controlled sphygmomanometer. The Task Force® Monitor has been shown to provide valid and reliable haemodynamic data (Fortin et al., 2001): the ICG system has been shown to be at least as reliable as the BioZ-PC (CardioDynamics, San Diego, CA, USA), while the continuous BP recordings are

comparable to the Finapres®, which are two widely used devices for the assessment of haemodynamic variables. In particular, as opposed to the Finapres® device, the Task Force® Monitor has the advantage of not requiring interruptions of the continuous BP measurement for the readjustment of the set point, because the set point is continuously readjusted throughout the assessment (Fortin et al., 2001).

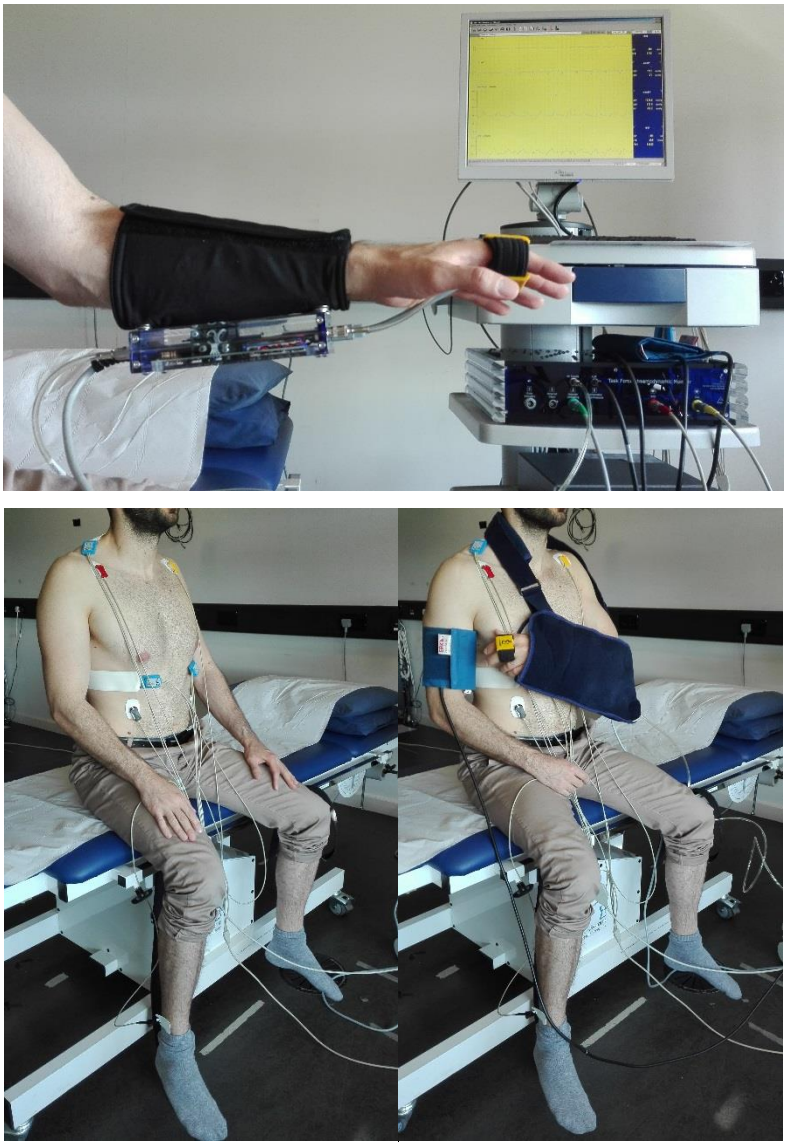
Before starting the HUT-60° test, participants were connected to the Task Force® Monitor as per manual instructions (Figure 2.7): they were donned with four ECG electrodes, three ICG electrodes, and a neutral electrode on the right foot. The respective skin parts were cleaned with some alcohol wipes before the electrodes were donned, and the researcher also made sure that the skin was absolutely dry before attaching all electrodes. The two superior ECG electrodes were placed in correspondence of the acromion processes on the shoulders, while the two inferior electrodes were placed on the abdomen, just above the umbilical region. The ICG electrodes consisted of 3 adhesive stripes to be placed on the patient's neck and thorax. More precisely, the superior ICG electrode was positioned in the area between the patient's neck and the hairline, while the remainder electrodes were positioned as parallel as possible at the lateral sides of the thorax at the xiphoid process level. The neutral electrode was attached on the right lower leg of the participants, just above the lateral malleolus.

The equipment for the measurement of continuous blood pressure consisted of a flying-V finger cuff (available in different sizes, e.g. small/medium/large), the Task Force® BP monitor, a removable Velcro fastener to fix the monitor to the forearm, and a compressed air hose. A flying-V finger cuff of appropriate size was fitted to the patient's index and middle fingers, as proximally as possible to ensure that the sensors weren't positioned on the fingers' knuckles. The finger cuff was subsequently connected to the continuous BP monitor, which was secured to the patient's forearm by means of the Velcro fastener. The continuous BP monitor was kept at heart level throughout the measurement.

The Task Force® sphygmomanometer was positioned on the patient's arm that was free from arteriovenous fistulas. Three cuff sizes were available, depending on the patient's arm circumference (small: arm circumference of 19-29cm, standard: arm circumference of 29-40cm, large: arm circumference over 40cm). The cuff was fit tightly to the upper

arm making sure that the air outlet was directly above the brachial artery, and that the lower edge of the cuff was approximately 2.5 cm above the elbow.

Figure 2.7. Task Force® Monitor: set up.



The HUT-60º test commenced with the participant lying in the supine position (Figure 2.8) on an electronically controlled tilt-table, with feet rested against a foot platform. Two Velcro straps placed over the participant's knees and hips secured the patients in position and prevented falling over during the tilt up manoeuvre. The participant was instructed

beforehand to lie quietly for 15 minutes, limiting any movement and avoiding speaking and sleeping during the measurement. The first 10 minutes were used to allow the calibration of the Task Force® Monitor and to ensure the haemodynamic equilibrium of the patient (Brignole et al., 2004). All variables of interest were then recorded for five minutes in the supine position. The electronically controlled table was subsequently tilted head-up by 60° (HUT-60°) with a smooth transition of approximately 4°/s (Benditt et al., 1996) for a period of five minutes during which time the patients' haemodynamic responses were continuously recorded (Figure 2.9). The HUT-60° protocol, as submitted to the REC, is further synthesised in Appendix IX.

Figure 2.8. HUT-60° test: supine position.

Figure 2.9. HUT-60° test: head-up tilt position.

2.5.1.3 Standardisation of pre-test conditions

All patients performed the HUT-60° on a non-dialysis day to minimise the acute effects of either fluid overload or fluid removal on data collected. The HUT-60° was performed in a quiet room with dim light and comfortable temperature between 18-22C^{o}.

On the assessment day, participants were advised to arrive in a rested state: they were instructed to have a light meal before testing and to be fasted for at least 2 hours. In addition, they were instructed not to smoke or consume caffeine/alcohol on the assessment day, and to avoid unaccustomed physical exercise on the 24 hours preceding testing. Medical staff and resuscitation equipment were immediately available in case of any possible adverse events. The assessment was conducted without the administration of any additional drugs but with patients being on their normal daily medication.

2.5.1.4 Test termination criteria

The HUT-60° was terminated upon completing the testing protocol described above or, alternatively, if any of the following events occurred during the assessment:

1. Induction of syncope or pre-syncope symptoms associated with marked hypotension or bradycardia or both (dizziness, palpitations, blurred vision, nausea, lightheadedness, headache);
2. Patient distress or discomfort;
3. Patient request;
4. Acute malignant arrhythmia (atrial fibrillation, supraventricular tachycardia, HR<40bpm);
5. SBP falling >80mmHg or falling rapidly;
6. Substantial reductions in BP (SBP>20 mmHg and/or DBP>10mmHg) compared to their baseline values without compensatory changes in other haemodynamic variables (HR, peripheral vascular resistance, stroke volume, cardiac output). This is defined as orthostatic syncope, where there are no compensatory adjustments due to failure of sympathetic tone to increase;
7. HR rising to ≥ 170/min;
8. Chest pain;
9. Asystole;
10. Any other adverse/unexpected event.

2.5.2 Baroreceptor reflex function indices

The baroreceptor reflex function, or baroreflex function, was assessed by means of the sequence method, a validated method which has been described to provide equivalent prognostic information to the invasive methods used to measure the baroreflex (Pinna et al., 2000).

The Task Force® monitor uses this method to assess the spontaneous activity of baroreceptors through the continuous beat-to-beat measurement of HR and BP. This method assesses the baroreflex function by considering the relationship between variations in SBP and simultaneous changes in R-R interval (RRI) (Parati et al., 2003).

This relationship provides information as to how many times a change in SBP is coupled with a concomitant change in RRI (n° of baroreceptor events), the steepness of the regression line between changes in mmHg of blood pressure and changes in milliseconds of RRI (baroreflex sensitivity), and how often the baroreflex produces a change in HR in response to a perturbation in BP (baroreceptor effectiveness index) (Di Rienzo et al., 2001).

2.5.2.1 Baroreceptor events: definition

A baroreceptor sequence or baroreceptor event is defined as the simultaneous coupling of a BP ramp with an increase or decrease of HR for at least 3 consecutive cardiac cycles (Kardos et al., 2001). In accordance with previous research, BP ramps were defined as either an increase or decrease in SBP of at least 1 mmHg for 3 consecutive heart beats: a "down-ramp" was defined as a decrease of at least 1 mmHg for three consecutive beats, while an "up-ramp" was defined as an increase of at least 1 mmHg for three consecutive beats. "Total-ramps" were defined as the sum of all down-ramps and up-ramps (Kardos et al., 2001). A baroreceptor event was then classified as the simultaneous coupling of a BP ramp with either an increase or decrease of the R-R interval (RRI) of at least 4 milliseconds (ms) (Pinna et al., 2015). More precisely, a "down-event" was classified as a concomitant decrease of continuous systolic blood pressure (contSBP) and RRI of at least 1 mmHg and 4ms respectively (-contSBP/-RRI sequence), while an "up-event" was classified as a concomitant increase of contSBP and RRI of at least 1 mmHg and 4ms respectively (+contSBP/+RRI sequence). "Total-events" were classified as the sum of all down-events and up-events.

2.5.2.2 Baroreflex sensitivity

The Task Force® Monitor software uses the sequence method to assess the sensitivity of the baroreflex (Parati et al., 1988). Baroreflex sensitivity (BRS) describes the steepness of the regression line between contSBP change in mmHg and the RRI change in ms, and it was automatically computed by the Task Force® Monitor software which averages the slopes of these regression lines (La Rovere et al., 2008).

2.5.2.3 Baroreceptor effectiveness index

The baroreceptor effectiveness index (BEI) represents how often the baroreflex produces a change in HR in response to a perturbation in BP (Di Rienzo et al., 2001). This index was introduced as a complementary measure to the BRS as it conveys additional information about the overall function of the baroreflex: while the BRS reflects the magnitude of the reflex HR response with respect to the amplitude of the SBP change only when the sinus node drive is activated, the BEI quantifies the number of times the baroreflex is effective in driving the sinus node (Di Rienzo et al., 2001).

The BEI was calculated as the ratio of occurred baroreceptor events and detected BP ramps expressed as a percentage {[(n° RRI/contSBP sequences)/n° BP ramps] *100}. This index can be characterised by three components: the "down-BEI" that represents the ratio of occurred down-events and detected down-ramps {[(n° -RRI/-contSBP sequences)/ n° down-ramps] *100}, the "up-BEI" that represents the ratio of occurred up-events and detected up-ramps {[(n° +RRI/+contSBP sequences)/ n° up-ramps] *100}, and the "total-BEI" that represents the ratio of occurred total-events and detected total-ramps {[(n° total RRI/contSBP sequences)/ n° total-ramps] *100}.

2.5.3 Haemodynamic regulation indices

In addition to the baroreflex measures, the following haemodynamic variables were recorded at rest, in the supine position, and during HUT-60°: RRI, HR, contSBP, continuous diastolic BP (contDBP), continuous mean BP (contmBP), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), and oscillometric BP (OscBP).

The Task Force® Monitor uses a 6-lead ECG for the measurement of RRI. Data was collected at 1000Hz with cut-off frequencies of 0.08Hz and 150Hz. HR was derived from the ECG with the algorithm: (60*1000)/RRI (Pan et Tompkins., 1985; Li et al., 1995).

SV, CO, and TPR were measured non-invasively by means of the Task Force® Monitor's ICG four-wire module, which operates at a measuring current of approximately 400μA at 40Hz (Fortin et al., 2006). ContSBP, contDBP, contmBP were measured by means of the beat-to-beat finger BP recordings through application of the vascular unloading technique (Parati et al., 2003). The finger BP recordings were self-calibrated against the brachial

artery BP, which was measured by means of the Task Force® Monitor's oscillometric BP cuff. This cuff was used to record OscBP at rest, during the supine position, and during HUT-60°.

2.6 Assessment of falls prevalence and incidence

2.6.1 Retrospective history of falls

The participants' history of falls, relative to the previous 12 months, was documented during the assessment visit by means of a standardised falls survey instrument (Appendix X). In this questionnaire, participants were asked to report any falls experienced in the previous 12 months. A fall was operationally defined as an unexpected event in which the participant comes to rest on the ground, floor, or lower level (Lamb et al., 2005). Participants were classified as having a positive history of falls if they reported at least one fall in the previous 12 months. The critical incident reporting of falls in the Renal Unit at Monklands Hospital was also used to double check whether or not the study participants had experienced any falls in the Renal Unit.

2.6.2 Prospective collection of falls related information

After completing the assessment visit, every participant was followed up for 12 months, by means of monthly face to face contacts to ensure as accurate documentation as possible of any falls and circumstances. The PhD researcher and a research nurse met with all the patients taking part in the study from Monklands Renal Unit and Victoria hospital Renal Unit once a month, during one of their usual HD treatment, and used a standardised falls diary (Appendix XI) to document the number of falls experienced, and the circumstances associated with these falls (e.g. timing of the fall, location, kind of activity resulting in the fall, precipitating factors, whether or not injuries were sustained, whether or not any action was taken). The prospective collection of falls-related information was used to classify the study participants as "fallers" and "non-fallers" to minimise the recollection bias that may be associated with self-reported information (Cummings et al., 1988; Ganz et al., 2005; Hauer et al., 2006). Participants were classified as fallers if they reported at least one fall over the course of the 12-month follow-up, or as non-fallers if they did not

experience any falls. Study termination criteria included reaching the end of the observational period (12 months after the first assessment visit), participants receiving kidney transplantation, or death.

It should also be acknowledged that a copy of the falls diary (Appendix XI) was provided to all research participants, at the time of baseline assessment, to encourage reporting of the falls experienced during follow-up. This approach has been particularly recommended by the Prevention of Falls Network Europe and Outcomes Consensus Group (Lamb et al., 2005) in order to minimise the recall bias. Participants were instructed to complete the falls diaries and to return them to the PhD researcher on a monthly basis (during follow-up visit). However, due to the initial very poor compliance of participants, the research team made the decision to discard this additional source of information and to rely only on the prospective information recorded by the PhD researcher during the monthly follow-ups. It is possible that a more integrated network of research nurses could have reduced the objective logistic issues encountered in collecting the falls diaries from study participants (Roberts et al., 2007).

2.6.3 Tinetti falls efficacy scale questionnaire

The Tinetti falls efficacy scale (FES) questionnaire was completed by all participants as a measure of fear of falling (Appendix XII). This questionnaire is a 10-item rating scale to assess an individual's perceived level of confidence in undertaking a range of activities of daily living without fear of falling (Tinetti et al., 1990). This scale is a widely used tool with good validity and reliability for the assessment of fear of falling (Tinetti et al., 1990; Huang et al., 2009). The researcher administered this questionnaire to participants during the assessment visit: they were asked to rate their fear of falling-related confidence when performing 10 common activities of daily living from 1 to 10, with 1 being extremely confident, and 10 being not confident at all. The final score was obtained by summing the 10 ratings and was used for data analysis purposes. Low falls-related self-efficacy, assessed by means of this questionnaire has been associated with impairments in performing activities of daily living, and with an increased risk of future falls in elderly people (Cumming et al., 2000).

2.7 Assessment visit

All frailty, physical and cardiovascular data were collected during a single assessment visit lasting about a couple of hours. Participants on a Monday-Wednesday-Friday dialysis schedule were assessed on a Tuesday, while participants on a Tuesday-Thursday-Saturday dialysis schedule were assessed on a Wednesday. The assessment visit took place in a designated room, equipped for the use of the Task Force® Monitor, in the Renal Units at Monklands and Victoria Hospitals. Resuscitation equipment was readily available, and nursing and medical staff support was also immediately available in case of emergency. On the day preceding the assessment, participants were provided with a leaflet reminding them to fast for at least two hours before the visit, as well as to refrain from consuming caffeine/alcohol, and to avoid unaccustomed physical exercise (Appendix XIII).

On the assessment day participants were explained all the procedures involved in the study and were given the chance to ask any information about the various measurements. Before commencing the cardiovascular and physical assessments, the researcher obtained the retrospective history of falls information from the participant and administered the Tinetti FES questionnaire. Participants then completed the SF-36 Health Survey, and the Short IPAQ questionnaires. Following the completion of all questionnaires, participants underwent the baroreflex and haemodynamic function assessment by means of HUT-60°: they were asked to undress their top half and they were donned with all the Task Force® Monitor electrodes as per manual instructions. After completing the testing protocol (described in section 2.5.1.2), they were returned to the supine position for an additional five minutes, during which time all the cardiovascular parameters (e.g. HR, BP) were monitored until they returned to the pre-test values. At this point the test was terminated and the participant was disconnected from the Task Force® Monitor.

The researcher subsequently instructed the participant on how to perform the handgrip test, and the three measurements with the dominant hand were taken. Following this test, participants were asked to remove their shoes for the balance assessments. It was then explained how to position the feet on the force platform and all verbal instructions relating to the testing protocol were given (described in section 2.3.3). Two measurements for each testing condition (EO and EC) were taken. After the balance assessment, participants

performed the isometric leg extension MVC test by means of the digital myometer (described in section 2.3.2). At this point, participants were asked to put their shoes back on and the testing session continued in a corridor purposively designated for the physical function tests, which was located right next to the assessment room. The gait speed, TUG and CSTS-5 tests were performed in this corridor. Following the physical functioning tests, the researcher explained the ActivPal™ wearing protocol and provided the participant with a leaflet reminding the main instructions on how to use and position the accelerometer. The monitor was then set up and given to the participant.

At the end of the assessment session, the researcher thanked the participant for his/her time and for contributing to the research project.

2.8 Biochemistry

Participants' clinical characteristics were extracted from the Scottish Electronic Renal Patient Record (SERPR). The following blood values were extracted from the SERPR at Monklands and Victoria hospitals: high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, haemoglobin (Hb), C-reactive protein (CRP), bicarbonate, sodium (Na), potassium (K), chloride (Cl), urea, phosphate, parathyroid hormone (PTH), albumin, adjusted calcium, urea reduction ratio (URR), creatinine, haematocrit. These values refer to the monthly bloods that are routinely collected from the HD patients at Monklands and Victoria hospitals: the values closest to the date of assessment (within 1-month period) of the different participants were taken for the data analysis.

2.9 Medications

The medications prescribed to the study participants, up until the date of assessment, were recorded from the SERPR at Monklands and Victoria hospitals. The use of antihypertensive and antidepressant medications was recorded as these classes of drugs might be associated with falls in HD patients (Desmet et al., 2005). In addition, before coming for the assessment, participants were provided with a leaflet (Appendix XII) reminding them to bring the most up to date list of medications with them on the day of

assessment. This list was double-checked by the researcher to highlight any possible discrepancies between the list of prescribed medications appearing on SERPR and the medications reported by the participant.

2.10 Comorbidities

The Charlson comorbidity index (CCI) (Charlson et al., 1987) was used to score the comorbidity levels of the study participants. The CCI is used to predict the 1-year mortality of an individual based on the presence or co-presence of several disease conditions: every disease is attributed a score of "1", "2", "3", or "6" depending on the severity of the pathology, as listed below.

- One point:
  - Myocardial infarction;
  - Congestive heart failure;
  - Peripheral disease;
  - Cerebrovascular disease;
  - Dementia;
  - Chronic pulmonary disease;
  - Connective tissue disease;
  - Peptic ulcer disease;
  - Mild liver disease;
  - Diabetes without end-organ damage;
- Two points:
  - Hemiplegia;
  - Moderate or severe renal disease;
  - Diabetes with end-organ damage;
  - Tumor without metastasis;
  - Lymphoma;
  - Leukemia;
- Three points:
  - Moderate or severe liver disease;
- Six points:
  - Metastatic solid tumor;
  - AIDS

The final CCI score is obtained by summing the points attributed to the disease conditions that the patient has. The medical conditions of the study participants were extracted from

SERPR and the CCI was calculated manually by applying the appropriate scores to their various disease conditions.

2.11 Anthropometric measurements

Body mass and height were measured on the day of assessment. Body mass was measured by means of the Bertec® BP5050 force platform to the nearest tenth of a kilogram: participants were asked to remove their shoes, empty their pockets and wear light clothing only during the measurement. They were instructed to stand centrally and as still as possible on the force platform, until a clear reading was obtained.

Height was measured by means of a portable stadiometer to the nearest 0.1 cm (Leicester Height Measure, Invicta plastics, Leicester). Participants were instructed to stand upright and barefoot on the stadiometer base of support and heels alignment was checked by the researcher. The head alignment on the Frankfort horizontal plane was also checked by ensuring the upper margin of the external auditory canal was at the same level of the lower margin of the eye socket. When the alignment was reached, the measuring rule was lowered until it made contact with the participant's head. The participant was therefore asked to step off the stadiometer and the measurement was recorded. The body mass index (BMI) was calculated from the body weight and height measurements by using the canonical formula: BMI= body mass (kg)/height $(m)^2$.

CHAPTER 3: ESTIMATES OF FALLS IN CKD-5 PATIENTS ON HD

Abstract

Background: CKD-5 patients on HD have commonly been reported to be at high risk of falls. While most studies conducted on HD patients have highlighted estimates of falls higher than in community-dwelling older adults, the findings on falls prevalence in this patient population vary greatly across studies, and some of them seem to suggest that the risk of falling in HD patients may not differ substantially from that of the general population. Therefore, we conducted a prospective observational study aiming to investigate whether CKD-5 patients on HD are at higher risk of falls compared to the community dwelling, non-uraemic, population.

Methods: We prospectively documented falls for 12 months in a convenience sample of prevalent HD patients from two research sites in North Lanarkshire and Fife, UK, and we calculated the prevalence of patients experiencing at least one fall per year, as well as the incidence of falls/person-year. We discussed how these estimates of falls compare to those of non-uraemic individuals living in the community. In addition, we critically reported the characteristics of the falls experienced by the study participants.

Results: Seventy-six patients were enrolled in this prospective investigation. Seven participants were lost to follow-up due to renal transplantation or death. Overall, 37.7% of patients experienced at least one fall during the 12-month follow-up. The total number of falls documented was 80, resulting in an incidence of 1.16 falls/person-year. The most common location of the falls reported was at home (72.5% of falls). The most common activity that led to falls was walking (31.3% of falls), and the most common precipitating factor was dizziness (36.3% of falls). The majority of the falls (61.3%) were non-injurious.

Conclusions: This prospective investigation confirms that CKD-5 patients on HD are at higher risk of falls compared to the community-dwelling, non-uraemic, population. The characteristics of the falls experienced suggest that low BP spells and orthostatic hypotension may be implicated in the aetiology of a high number of falls in CKD-5 patients on HD. Worryingly, the large majority of falls remains unreported in this patient population.

3.1 Introduction

In Lanarkshire, Scotland, 33835 falls were documented in 2006 (General Register Office for Scotland (GROS), 2006), and 3150 people aged 60 years and older presented to the A&E with fractures as a direct result of a fall. Of these fractures, 724 involved the neck of femur, for a cost of £8.8 million to acute services and over £9 million in social care, and it was suggested that a quarter to one third of these falls could have been prevented.

In the last 15 years, several observational studies have investigated falls prevalence, fall-related injuries, and relative risk factors in CKD-5 patients undergoing HD therapy (Roberts et al., 2003; Cook et al., 2005; Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; Abdel-Rahman et al., 2011; Rossier et al., 2012; McAdams-DeMarco et al., 2013; Kutner et al., 2014; Polinder-Bos et al., 2014; Farragher et al., 2014; Delgado et al., 2015; Noto-Kadou-Kaza et al., 2015; Wang et al., 2017; Kono et al., 2018), and a recent literature review on falls in CKD patients concluded that HD patients are a patient group at high risk of falls (Lopez-Soto et al., 2015). However, the prevalence of patients experiencing at least one fall per year has been reported to vary greatly from one study to another, as 16.7% (Wang et al., 2017) to 55% (Polinder-Bos et al., 2014) of patients on HD have been described to report at least one fall in prospective cohort studies with a 12-month follow-up.

The WHO global report on falls prevention in older age (2008) states that about 30% of community-dwelling individuals aged 65 years or older incur in at least one fall every year, and are classified as a segment of the population at higher risk of falls. Theoretically, such a prevalence would constitute the null hypothesis in the context of comparing falls estimates between older CKD-5 patients on HD and community dwelling, non-uraemic, age-matched individuals, as one would expect to find a prevalence of fallers higher than 30% in this group of patients in order to classify them at higher risk of falling compared to the general population.

While many studies conducted on HD patients older than 65 years of age reported a higher yearly prevalence of fallers, ranging from 38% to 55% (Roberts et al., 2007; Abdel-Rahman et al., 2011; Farragher et al., 2014; Polinder-Bos et al., 2014), other studies (Roberts et al., 2003; Cook et al., 2005; Wang et al., 2017) found a lower prevalence,

ranging from 16.7% to 27.7%, which seem to partly suggest that the falls' risk profile of older HD patients may not differ substantially from that of the community-dwelling population of older adults.

Nevertheless, the risk of falling in a given population cannot be characterised exclusively in terms of prevalence of fallers, namely the proportion of subjects experiencing at least one fall per year. The number of falls experienced by every person is also a potentially important factor, as a higher number of falls is more likely to result in adverse outcomes such as fractures, hospitalisation, and even death (Abdel-Rahman et al., 2011; Rossier et al., 2012). This factor has been considered in several prospective cohort studies conducted on HD patients, where the number of falls experienced by the study participants was recorded during the follow-up period in order to measure the incidence of falls/person-year (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; Abdel-Rahman et al., 2011; McAdams-DeMarco et al., 2013; Farragher et al., 2014; Polinder-Bos et al., 2014). The results from these studies generally indicate that the incidence of falls/person-year in HD patients is greater than in community-dwelling older adults. Six out of 7 studies reported that HD patients had an incidence of falls 1.5 (McAdams-DeMarco et al., 2013) to 3.5 times (Roberts et al., 2007) higher than community-dwelling individuals aged 65 years or older (O'Loughlin et al., 1993), while only one study found a 1.2 times lower incidence of falls in HD patients compared to community-dwelling older adults (Abdel-Rahman et al., 2011).

Although the majority of observational studies conducted on HD patients seem to suggest that, overall, they are at increased risk of falls compared to the general population (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; McAdams-DeMarco et al., 2013; Kutner et al., 2014; Farragher et al., 2014; Polinder-Bos et al., 2014; Noto-Kadou-Kaza et al., 2015), as also concluded by a recent literature review (Lopez-Soto et al., 2015), contrasting results on falls estimates from other studies (Roberts et al., 2003; Cook et al., 2005; Abdel-Rahman et al., 2011; Wang et al., 2017) conducted in HD populations do not seem to support this finding. In addition, there is a lack of information on the characteristics of the falls experienced by patients, as only a few studies provided detailed information on the circumstances accompanying the fall events (Chapter 1, paragraph

1.2.2.5), and only two studies described the kind of activity leading to falls (Cook et al., 2006; Farragher et al., 2014), which could convey important information on the aetiology of falls in this patient group.

The main objective of this chapter was to contribute to the current body of knowledge on the epidemiology of falls in CKD in order to establish whether the risk of falling in CKD-5 patients on HD is increased compared to the non-uraemic population. We hypothesised that 1) the prevalence of participants experiencing at least one fall over 12 months and, 2) the incidence of falls/person-year will be indicative of an increased risk of falling compared to the estimates of falls from the non-uraemic population. The secondary aim of this chapter was to critically report the characteristics of falls experienced by the study participants in order to delineate the most common circumstances (location, activities, precipitating factors, and consequences) around the fall events.

3.2 Materials and methods

3.2.1 Study design

We conducted a prospective investigation of the prevalence of people experiencing at least one fall during a 12-month observational follow-up, as well as the incidence of falls/person-year in a group of prevalent HD patients.

3.2.2 Setting

The study was conducted in two Renal Units located in North Lanarkshire and Fife, United Kingdom, between October 2015 and August 2018. Recruitment started in October 2015 and continued on a rolling basis until December 2017, while the observational follow-ups ran from November 2015 to August 2018. Ethical approval was granted, as detailed in Chapter 2, paragraph 2.1.1.

3.2.3 Participants

A convenience sample of ambulatory CKD-5 patients undergoing HD therapy thrice weekly were recruited from the two dialysis units at Monklands Hospital, Airdrie, NHS

North Lanarkshire, and Victoria Hospital, Kirkcaldy, NHS Fife. Inclusion and exclusion criteria are detailed in Chapter 2, paragraph 2.1.2.

3.2.4 Falls

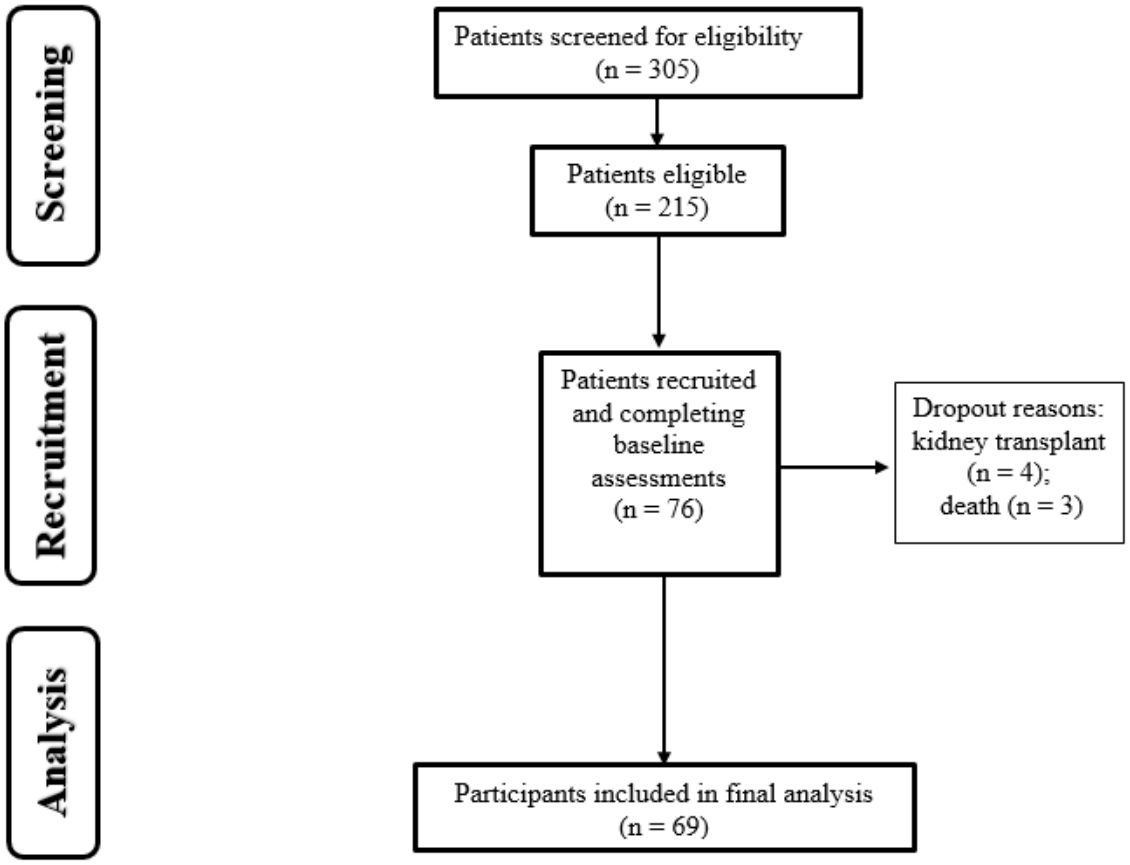
A fall was operationally defined as an unexpected event in which the participant comes to rest to the ground, floor, or lower level (Lamb et al., 2005). The PhD researcher and two research nurses administered a falls questionnaire, once a month for a period of 12 months (as detailed in Chapter 2, paragraph 2.6.2), to all study participants during dialysis. The number of falls were recorded during every follow-up visit along with the characteristics of these falls (i.e. location, activities, precipitating factors) and their consequences. In addition, the retrospective history of falls of the study participants was also documented at the time of enrolment in the study (as detailed in Chapter 2, paragraph 2.6.1).

3.3 Results

3.3.1 Recruitment and loss to follow-up

Three hundred and five patients undergoing outpatient HD therapy at the two Renal Units were screened for eligibility by members of the renal team. Of these, 215 patients were deemed eligible to participate and therefore approached for recruitment and consenting. The recruitment rate was 35.3%, with 76 patients agreeing to participate in the study. Nine patients (11.8%) were lost to follow-up due to renal transplantation (n= 4; 5.3%) and death (n= 5; 6.6%), although two of these patients were retained in the calculation of the falls estimates due to the fact that they had experienced falls during the prospective observational period before they were lost to follow-up. Therefore, a total of 69 patients completed the prospective follow-ups and were included in the calculation of the falls estimates (Figure 3.1). In addition, all 76 study participants completed the falls survey documenting their history of falls in the previous 12 months.

Figure 3.1. Participant recruitment: flow chart.



3.3.2 Demographic and clinical characteristics

The demographic and clinical characteristics of study participants are summarised in Table 3.1.

Table 3.1. Demographic and clinical characteristics of study participants: results are expressed as percentages for categorical variables and mean ± SD for continuous data.

Variables	All patients (69)	Fallers (26)	Non-fallers (43)	P-value
Demographic characteristics				
Sex, M (n) (%)	38 (55.1)	11 (42.3)	27 (62.8)	0.097
Age (years) (SD)	61.7 (13.3)	58.3 (14.1)	63.8 (12.6)	0.151
Body mass (Kg) (SD)	80.3 (18.7)	75.7 (18.6)	83.1 (18.5)	0.114
Height (cm) (SD)	166.2 (9)	166 (9)	166.3 (9)	0.892
BMI (Kg * m^{-2}) (SD)	29.1 (6.4)	27.6 (7)	30 (5.9)	0.144
Clinical history				
Dialysis vintage (days) (SD)	713 (714)	732 (636)	701 (765)	0.465
CCI (score) (SD)	5.3 (2.2)	5.1 (2.1)	5.4 (2.3)	0.639
Primary renal disease (n) (%)				
Diabetic nephropathy	17 (25)	7 (26.9)	10 (23.8)	0.773
Glomerulonephritis	13 (19.1)	5 (19.2)	8 (19)	1.000
Polycystic kidney	6 (8.8)	0 (0)	6 (14.3)	0.075
Renovascular or hypertensive	6 (8.8)	0 (0)	6 (14.3)	0.075
Other	14 (20.6)	6 (23.1)	8 (19)	0.690
Uncertain aetiology	12 (17.6)	8 (30.8)	4 (9.5)	0.046
Type of vascular access (n) (%)				
Arteriovenous fistula	45 (64.7)	16 (61.5)	29 (66.7)	0.667
Central-venous	24 (35.3)	10 (38.5)	14 (33.3)	0.667
Inter-dialytic weight gain (Kg) (SD)	1.6 (1.2)	1.6 (1)	1.6 (1.4)	0.923
Prescribed medications				
Medications (n°) (SD)	11.8 (3.4)	12.4 (3.3)	11.5 (3.5)	0.262
Beta blockers use (n) (%)	35 (50)	11 (42.3)	24 (54.8)	0.318
ACE-inhibitors use (n) (%)	5 (7.4)	2 (7.7)	3 (7.1)	1.000
Ca-channel blockers use (n) (%)	40 (57.4)	13 (50)	27 (61.9)	0.335
AngII-receptor antagonists use (n) (%)	11 (16.2)	3 (11.5)	8 (19)	0.512
Alpha blockers use (n) (%)	22 (32.4)	10 (38.5)	12 (28.6)	0.397
Antihypertensive use (n) (%)	58 (83.8)	21 (80.8)	37 (85.7)	0.737
>1 antihypertensive use (n) (%)	36 (51.5)	11 (42.3)	25 (57.1)	0.234
Opiates use (n) (%)	13 (19.1)	3 (11.5)	10 (23.8)	0.342
Antidepressants use (n) (%)	23 (33.8)	13 (50)	10 (23.8)	0.027
Diuretics use (n) (%)	23 (33.8)	6 (23.1)	17 (40.5)	0.141

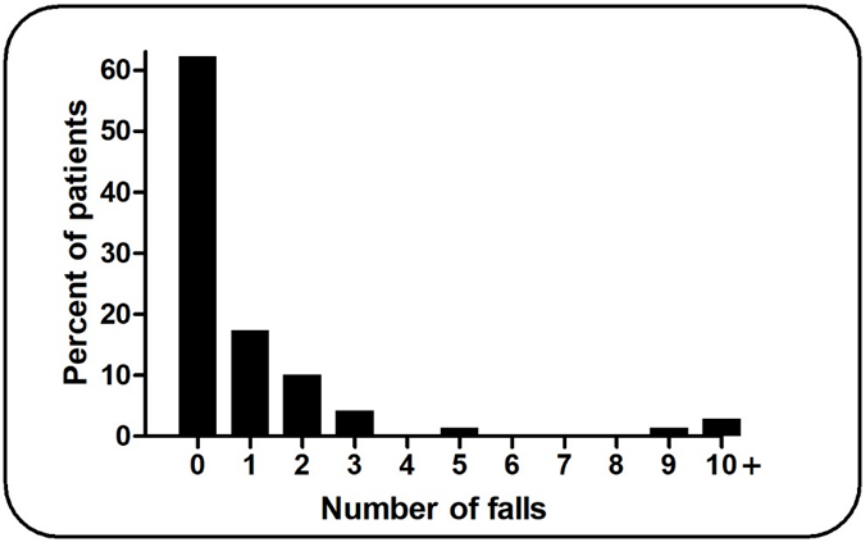
Laboratory values				
Hb (g/dL) (SD)	11.2 (1.2)	11 (1)	11.2 (1.2)	0.317
CRP (mg/L) (SD)	25.8 (45.4)	37.6 (59.2)	18.3 (32.7)	0.027
Bicarbonate (mmol/L) (SD)	21.2 (3.2)	21.5 (3.1)	21.1 (3.4)	0.546
Na (mmol/L) (SD)	139 (2.8)	138.4 (3.3)	139.4 (2.4)	0.388
K (mmol/L) (SD)	4.6 (0.7)	4.6 (0.7)	4.6 (0.6)	0.992
Urea (mg/dL) (SD)	16.4 (5.1)	15.7 (6.1)	16.7 (4.5)	0.276
Phosphate (mmol/L) (SD)	1.5 (0.6)	1.5 (0.6)	1.5 (0.5)	0.978
PTH (ρmol/L) (SD)	27.2 (32.1)	28.9 (43.4)	26.2 (23.1)	0.586
Albumin (g/L) (SD)	37.1 (4.3)	36.1 (5.2)	37.7 (3.7)	0.146
Adjusted calcium (mmol/L) (SD)	2.4 (0.1)	2.3 (0.1)	2.4 (0.1)	0.511
URR (%) (SD)	71.1 (6.2)	71.1 (7.7)	71 (5.1)	0.994
Creatinine (μmol/L) (SD)	638.1 (161.3)	592(175.7)	666 (147.1)	0.064

Abbreviations: SD: standard deviation; BMI: body mass index; CCI: Charlson comorbidity index; ACE: angiotensin-converting enzyme; Ca: calcium; AngII: angiotensin II; Hb: hemoglobin; CRP: C-reactive protein; Na: sodium; K: potassium; PTH: parathyroid hormone; URR: urea reduction ratio.

3.3.3 Estimates of falls

During the 12-month follow-up, 26 of 69 patients (37.7%) experienced at least one fall, of which 14 (53.8%) experienced multiple falls. The distribution of number of falls occurred during the prospective observational period is displayed in Figure 3.2. The maximum amount of falls experienced by one patient was 21, and a total of 80 falls were recorded, resulting in an incidence of 1.16 falls/patient-year. In addition, in the retrospective history of falls survey, 33 of 76 patients (43.4%) reported falling at least once in the previous 12 months and, overall, 44 of 76 patients (57.9%) reported either a fall in the previous year or during follow-up.

Figure 3.2. Distribution of number of falls in the study participants.



3.3.4 Characteristics of falls

3.3.4.1 Location of falls

The most common location where the study participants experienced falls was their home, as 17 of the 26 patients who suffered falls (65.4%) reported falling at least once at home. In addition, 13 out of 26 (50%) experienced at least one fall outdoors, and 7 (26.9%) reported at least one fall in another public site. Two patients out of the 26 fallers (7.7%) reported falling in all these locations at least once during the study period. Overall, 58 out of 80 falls (72.5%) were sustained at home, 15 (18.8%) occurred outdoors, and 7 (8.8%) in another public site (Figure 3.3).

3.3.4.2 Activities leading to falls

The most common activity leading to falls was walking, as 19 of the 26 patients who suffered falls (73.1%) reported falling while walking at least once over the study period. Other commonly reported activities leading to falls were getting up from either a supine or a sitting position to upright standing, turning around, and walking up or down the stairs. More precisely, 12 out 26 fallers (46.2%) reported falling during the transition from a supine/sitting position to upright standing at least once, five (19.2%) reported falling at

least once while turning around, and the remaining five (19.2%) reported experiencing one fall while walking up or down the stairs at least one time.

Overall, 25 out of 80 falls (31.3%) were experienced by the study participants while they were walking (18.8% of all falls occurred while walking indoors, and 12.5% occurred outdoors). Seventeen out of 80 falls (21.3%) occurred during the transition from a supine/sitting position to upright standing (6.3% from the supine position, and 15% from a sitting position). Twelve falls (15%) occurred while patients were turning around and a further five falls (6.3%) happened while they were walking up (2.5%) or down (3.8%) the stairs. In addition, 21 falls (26.3%) were caused by other activities, namely unspecified falls from the standing position (6.3%), tripping over an obstacle (5%), bending over to pick up an object (3.8%), slipping on ice (3.8%), sitting down (1.3%), hoovering (1.3%), alcohol-related (1.3%), or unknown (i.e. no recollection) (3.8%).

3.3.4.3 Precipitating factors

The precipitating factors represent the predominant perceived cause/symptomatology reported by the patient when describing the fall event. The most commonly reported factors were dizziness/passing out, loss of balance/unsteadiness of the legs, and environmental factors. More specifically, 12 out of the 26 fallers (46.2%) reported either dizziness or passing out as the predominant factor leading to at least one fall during the study period. Fifteen out of 26 (57.7%) reported either a loss of balance or unsteadiness of the legs, and 13 (50%) reported factors such as a slip or a trip due to environmental hazards.

Overall, 33 out of 80 falls (41.3%) were accompanied by dizziness symptoms or passing out (36.3% due to dizziness, and 5% due to a loss of consciousness). Twenty-five out of 80 falls (31.3%) were accompanied by a loss of balance or unsteadiness of the legs (18.8% due to loss of balance, and 12.5% due to unsteadiness of the legs). Sixteen falls (20%) were due to a slip or trip arising from environmental hazards (11.3% due to a slip, and 8.8% due to a trip). In addition, the symptomatology of six of the 80 falls (7.5%) was unspecified/unclear.

3.3.4.4 Timing of falls

In the sub-group of study participants from the NHS Fife research site, we also extracted information on the timing of the falls experienced, which was classified in relation to whether these falls occurred on a non-HD day, or on a HD day (pre or post-HD) as reported in previous studies (Desmet et al., 2005; Cook et al., 2006; Abdel-Rahman et al., 2011; Rossier et al., 2012; Polinder-Bos et al., 2014).

Nine patients out of the 24 from this research site (37.5%) experienced falls, eight of which (33.3%) reported having at least one fall on a non-HD day, while four (16.7%) and one (4.2%), respectively, reported falling at least once pre-HD and post-HD. Overall, 16 of the 23 falls recorded at this research site (69.6%) occurred on a non-HD day, while five (20.8%) and two (8.3%) occurred pre-HD and post-HD respectively.

3.3.4.5 Consequences of falls

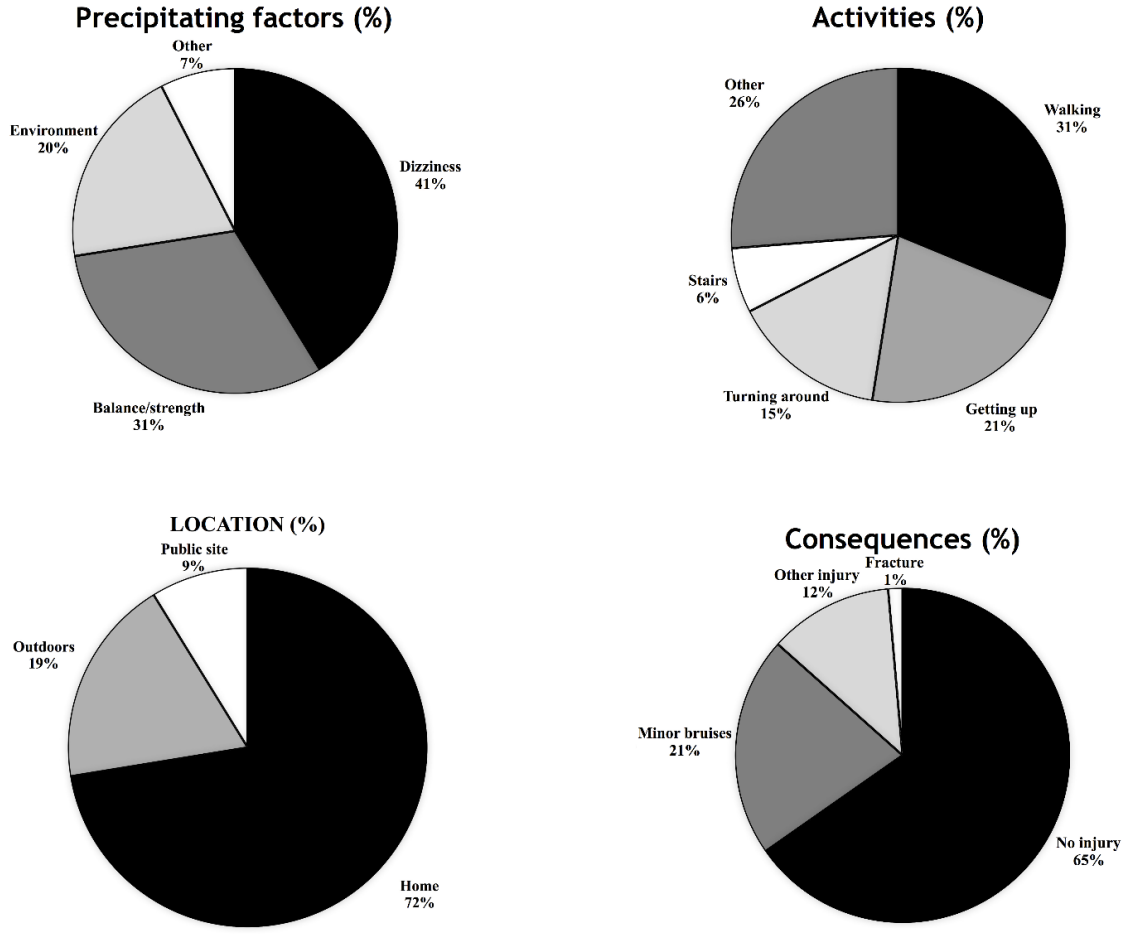
The consequences of a fall were documented in terms of injury sustained by the patient, and in terms of whether or not healthcare was sought to treat these injuries. The majority of falls experienced by the study participants (61.3%) were non-injurious, while the remaining falls resulted in minor/major injuries that were classified as bruising, non-specified soft tissue/joint injuries, and fracture. Thirteen out of the 26 fallers (50%) reported bruising to a variety of areas of the body at least once as a result of the falls experienced during the study period. Eight patients (30.8%) reported a non-specified soft tissue/joint injury, and one patient (3.8%) suffered a fracture.

Overall, 16 of the 80 falls recorded (20%) resulted in various bruises in the following body areas: knee (5%), back (3.8%), leg (3.8%), hand (2.5%), forearm (1.3%), chest (1.3%), buttocks (1.3%), and eye (1.3%). Nine falls (11.3%) resulted in other soft tissue/joint injuries in the following locations: face (2.5%), arm (2.5%), back (2.5%), knee (2.5%), unspecified location (1.3%). One fall (1.3%) was complicated by a fracture of the shoulder. Moreover, four patients (15.4%) reported banging the head at least once as a result of the falls experienced.

As far as healthcare required is concerned, eight falls (10%) were reported to the GP/medical care team and either treatment or medical advice was provided. Three patients

(11.5%) were hospitalised following the fall experienced (one patient required an X-ray, one required medical treatment, and one was hospitalised with sepsis and confusion). Overall, three falls (3.8%) required hospitalisation.

Figure 3.3. Summary of characteristics of falls experienced by the study participants.



3.3.5 Critical incident reporting of falls at Monklands Hospital

We also reviewed the critical incident reporting of falls in one of the two research sites (Monklands Hospital, NHS North Lanarkshire) as a secondary source of information about falls occurring within the hospital environment. The critical incident reporting of

falls at Monklands hospital is routinely performed by the renal nursing staff, who are responsible for documenting all accidental falls occurring in the Renal Unit.

In the 12 months preceding the start of the study, between October 2014 and October 2015, 48 falls were recorded in the Renal Unit. These falls were experienced by 39 patients, three of whom participated in the study. Therefore, three out of the 52 study participants from Monklands hospital (5.8%) had a history of falls occurring in the Renal Unit, in the previous 12 months.

The severity of the documented falls was graded by the nursing staff, as per standard NHS protocol, in three categories of injury: category 3 (CAT3) representing all of those falls which resulted in no injury and requiring no medical attention, category 2 (CAT2) representing falls resulting in minor injuries (e.g. haematomas, abrasions, cuts) and/or requiring a minor level of medical attention or treatment, and category 1 (CAT1) representing falls complicated by major injuries (e.g. fractures, death) and requiring more urgent medical attention or treatment. Overall, 36 falls (75%) were classified as non-injurious (CAT3), 11 falls (22.9%) resulted in minor injuries (CAT2), and one fall (2.1%) was complicated by a major injury (CAT1).

3.4 Discussion

We hypothesised that the estimates of falls in HD patients, as defined by the prevalence of participants experiencing at least one fall over 12 months and the incidence of falls/person-year, would be indicative of an increased risk of falling compared to those reported in non-uraemic individuals living in the community.

The prevalence of study participants reporting at least one fall over 12 months was 37.7%, an estimate somewhat higher than the yearly prevalence of community-dwelling older adults who fall at least once (30%), as outlined by the WHO global report on falls (2008). Additionally, the prevalence emerging from the study is also considerably higher than the prevalence of community-dwelling individuals, aged 40 years and older, reporting at least one fall in the past year (7.9% to 12.1%), as observed in larger epidemiological studies (Agrawal et al., 2009; Schumacher et al., 2014), and also higher than the prevalence of middle-aged women with a history of falls in the previous 12 months (20.5% to 30.7%),

as described in a more recent study (White et al., 2018). Moreover, 43.4% of the study participants reported that they had experienced at least one fall in the previous year, which is also indicative of an increased risk of falling compared to the community-dwelling, non-uraemic population.

Analogously, the number of falls experienced by the study participants during the prospective follow-up period equated to an incidence of 1.16 falls/person-year, approximately 2.3 times higher than in community-dwelling older adults (O'Loughlin et al., 1993). The observations that both the falls estimates emerging from this prospective investigation are higher than those relative to the non-uraemic, elderly population, and that our study participants were generally even younger than 65 years old (mean age= 61.1 years), strongly support the hypothesis that CKD-5 patients on HD are at higher risk of falls compared with the community-dwelling, non-uraemic, age-matched population.

Although the study was conducted in a small cohort of patients, our findings are broadly in agreement with those of larger observational studies. For instance, Desmet et al., (2005), reported a yearly incidence of 1.18 falls/person-year for their HD patients, which is very similar to the estimate observed in our study (1.16 falls/patient-year). Additionally, the proportion of patients who experienced at least one fall during the 12-month follow-up (37.7%), is also very similar to that reported in previous research (38%) (Roberts et al., 2007).

Interestingly, the study findings are aligned with the large majority of those studies that investigated falls prospectively by means of monthly, or even more frequent, observational follow-ups (Table 1.4 & Table 1.5, Chapter 1). Six out of seven of these studies reported a prevalence of patients experiencing at least one fall greater than the 30% estimate of community-dwelling older adults (WHO, 2008), with a range of 34% to 55% (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; Farragher 2014; Polinder-Bos et al., 2014; Kono et al., 2018). Only one study out of seven with such characteristics, i.e. prospective design and a minimum monthly follow-up frequency, reported a slightly lower prevalence of fallers (26.3%), although it should be acknowledged that the mean age of the study participants in this investigation was less than 65 years old (Abdel-Rahman et al., 2011).

In addition, the prevalence of fallers emerging from the current investigation appears to be higher than that previously reported in retrospective observational studies (24% to 28.4%). However, it is noteworthy that these published prevalences were based on estimates derived from self-reports of falls occurrence in the previous 12 months (Roberts et al., 2003; Cook et al., 2005; Kutner et al., 2014; Wang et al., 2017), as summarised in Table 1.4, Chapter 1. This difference might be explained in light of the fact that retrospective self-reporting of falls is often subject to recall bias that leads to under-reporting (Hauer et al., 2006). Particularly, observational studies with retrospective design are more subject to this kind of misreporting given the longer recall interval (Ganz et al., 2005). For instance, while all of the retrospective studies assessed whether patients had fallen or not by means of a single-item falls survey (e.g. "have you had any falls in the past year?"), we prospectively followed-up the study participants on a monthly basis for 12 months, in an attempt to minimise this bias, which is likely to have resulted in a more accurate estimation of the prevalence of fallers (Hauer et al., 2006).

Similarly, the incidence of falls/person-year emerging from this investigation (1.16 falls/person-year; 2.3 times higher than non-uraemic older adults) is in agreement with the findings of the large majority of studies that reported, directly or indirectly, this measure (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; McAdams-DeMarco et al., 2013; Kutner et al., 2014; Farragher et al., 2014; Polinder-Bos et al., 2014). Therefore, our findings on falls prevalence and incidence in HD patients seem to be representative of this patient group, and results from this study may be generalised to the general population of CKD-5 patients undergoing HD therapy.

The secondary aim of this investigation was to report the characteristics of the falls experienced by study participants in order to document the circumstances of the fall events in the CKD-5 population on HD. The critical reporting of these circumstances is often neglected and very little information is available from prospective cohort studies conducted on HD patients (Lopez-Soto et al., 2015), nevertheless this kind of data may convey useful information on the aetiology of falling in this patient population.

The results from the falls survey administered to the study participants during every follow-up visit revealed that the most common location of the falls experienced was at

home (72.5% of falls). In addition, it was evident that the most common activity leading to the falls was walking (31.3% of falls), the most common precipitating factor was dizziness (36.3% of falls), and the majority of falls (61.3%) were non-injurious (Figure 3.3).

The findings on the location of falls is in agreement with all the studies that reported this kind of information, as 54.2% to 82% of the falls recorded in these studies occurred at home, which also resulted to be the most common location (Desmet et al., 2005; Rossier et al., 2012; Polinder-Bos et al., 2014). On the other hand, the relatively small proportion of falls occurring outdoors (18.8%), as observed in our study, may reflect the well-known sedentary habits of HD patients (Delgado et al., 2012).

The most common activity preceding falls, as reported by the study participants, was walking (31.3% of falls). This figure is also in agreement with the only two studies that reported this information (Cook et al., 2006; Farragher et al., 2014). Particularly, these studies revealed that 29.8% (Cook et al., 2006) and 51% (Farragher et al., 2014) of the falls recorded during the prospective follow-up occurred while walking indoors, which may also reflect the high proportion of falls occurring at home. However, it should also be noted that a high number of falls, in our study, were preceded by a transition from the supine/sitting position to upright standing (21.3% of falls), or by a sudden rotation (15% of falls occurred when turning around). This information is interesting in light of the symptoms reported by the study participants as precipitating factors: 36.3% of the falls were precipitated by dizziness, which was also the factor most commonly reported. Therefore, the observations that about 40% of the falls occurred during a sudden change of body position, and were accompanied by dizziness seem to indirectly support the hypothesis put forward by previous research that the aetiology of a high number of falls in HD patients may be due to low BP spells and/or orthostatic hypotension (Roberts et al., 2003). Moreover, this finding seems to be consistent with the results of Cook et al., (2006), who also reported that 33% of the recorded falls occurred during the transition from the supine/sitting position to upright standing.

Although some researchers hypothesised that during the post-HD timeframe patients might be particularly susceptible to an increased risk of dizziness, postural hypotension,

and potentially falls, due to the fluid shifts associated with dialysis (Roberts et al., 2003), most studies did not highlight any relationship between the post-HD timeframe and falls (Cook et al., 2006; Abdel-Rahman et al., 2011; Rossier et al., 2012; Polinder-Bos et al., 2014). The results of our investigation are also aligned with these studies. Even though we collected this information from one research site only (with only 9 fallers), the descriptive analysis revealed that most falls (69.6%) occurred on non-dialysis days, and only 8.3% were reported post-HD. Ultimately, the relationship between the post-HD timeframe and the occurrence of falls may be confounded by the fact that HD patients may experience post-dialysis fatigue, which is associated with sedentary behaviour (Gordon et al., 2011). Therefore, although HD patients may be at higher risk of dizziness and postural hypotension after HD (Roberts et al., 2003), the post-HD sedentary behaviour may mediate the risk of falling by reducing it due to the actual lack of movement.

The findings on the consequences of falls indicate that the large majority of these were non-injurious, as 61.3% of falls resulted in no consequences and 20% in minor bruises only. Only one patient (3.8%) suffered a fracture as a result of falls, a similar estimate to the findings from previous studies reporting that 4% to 6% only of HD patients experienced a fracture following a fall (Cook et al., 2005; Cook et al., 2006; Farragher et al., 2014). Additionally, the critical incident reporting at Monklands Hospital revealed that only 2.1% of the falls recorded during the 12 months preceding the study initiation resulted in a major injury, which indirectly highlights the small proportion of falls that result in a severe accident. This observation should be considered by nephrologists because very often falls are brought to medical attention only when a severe injury is sustained as a result of the fall (Rossier et al., 2012), and many falling accidents remain undetected or underreported (Hauer et al., 2006). Our investigation revealed that only 10% of the falls experienced by the study participants were reported to the GP/medical care team, while the remaining 90% would have remained completely undetected if they had not been documented during the prospective follow-up period. Moreover, the number of falls documented in the study participants from Monklands Hospital (57) was higher than the number of falls documented by means of the critical incident reporting at the same hospital (48) in the previous 12 months: it should be kept in mind that only a small sample

of HD patients (52) took part in our study from this research site, while the critical incident reporting of falls by means of the nursing staff has a much larger constituency of patients (> 200) because it aims to document all falls experienced by any patient (HD or not) in the renal ward. Altogether, these observations strongly suggest that the majority of falls suffered by HD patients are not commonly reported in hospital records.

3.4.1 Limitations

First of all, the patient sample was relatively small compared to larger observational studies and this could have resulted in a potentially larger inflation/deflation of the falls estimates than if the patient sample was larger. However, the findings on falls prevalence and incidence seem to be representative of this patient population, and the results from the study may be generalised to the population of CKD-5 patients on HD.

Secondly, the documentation of falls was based on self-reported information, and a previous systematic review has highlighted how recalling information about falls might be subjected to misreporting (Hauer et al., 2006). Although we sought to minimise this bias by prospectively following up the participants every month, rather than retrospectively, (Cummings et al., 1988), it is still possible that a small proportion of falls might have been misreported, potentially resulting in some degree of error in the estimates of falls obtained.

3.4.2. Conclusions

The results from this prospective investigation confirm that CKD-5 patients on HD are at higher risk of falls compared to the community dwelling, non-uraemic, population, as evidenced by the higher prevalence of patients experiencing at least one fall per annum, as well as the higher incidence of falls/person-year. The high proportion of falls occurring during a change in body position, and precipitated by dizziness, suggest that low BP spells and orthostatic hypotension may be implicated in the aetiology of a high number of falls in CKD-5 patients on HD. Worryingly, the large majority of falls remains unreported in this patient population.

CHAPTER 4: FRAILTY, PHYSICAL FUNCTION AND FALLS IN CKD-5 PATIENTS ON HD

Abstract

Background: Frailty and poor physical function are common in CKD-5 patients undergoing HD therapy, and they may be implicated in the aetiology of falls in this patient population. Therefore, we explored the relationship between frailty, physical function and falls in a convenience sample of CKD-5 patients on HD.

Methods: Seventy-six prevalent HD patients recruited from two Renal Units were enrolled in this cross-sectional study. Participants were classified as "fallers" and "non-fallers" and completed a comprehensive physical function assessment consisting of objectively measured physical activity (PA), handgrip strength, isometric leg extension strength, gait speed, timed up and go (TUG), 5 repetitions chair sit to stands (CSTS-5), and postural balance testing by means of a force platform. In addition, participants were classified as "frail" or "non-frail" by means of the Fried's frailty phenotype. All assessments were performed during a single visit on a non-HD day. The differences in frailty status and physical function between fallers and non-fallers were preliminarily analysed by means of a Chi-square test and either parametric (independent t-tests) or non-parametric (Mann-Whitney U) independent comparisons, as appropriate. The association of frailty/physical function and falls (yes or no) was analysed by means of logistic regression. Statistical limits for interpretation were set at an alpha level of $p = .05$.

Results: Patients classified as fallers had significant lower objectively measured levels of PA, such as time spent standing (2.1±1.1h vs 2.7±1.2h, p= 0.034), time spent stepping (0.6±0.3h vs 0.8±0.4h, p= 0.016), and number of daily steps (2566±1462 vs 3731±1966, p= 0.015) compared to non-fallers. In addition, fallers had a worse postural balance performance in seven and nine out the nine variables assessed in eyes open (EO) and eyes closed (EC) conditions. No significant differences in strength and physical function tests were detected between fallers and non-fallers. Frailty (OR: 3.15, 95% CI: 1.04-9.54, p= 0.04) and postural balance (OR: 1.14, 95% CI: 1.02-1.28, p= 0.022) were associated with increased odds of falling in multivariate logistic regression analysis.

Conclusions: This cross-sectional investigation indicates that frailty and postural balance are associated with falls in CKD-5 patients undergoing HD therapy. Postural balance is a physical function outcome at least partially independent from frailty, and it may represent an additional risk factor for falls. Further research is warranted to identify which physical function measures may be more closely associated with falls in this patient population.

4.1 Introduction

Frailty and poor physical function are associated with worse outcomes such as hospitalisations and increased mortality in people living with CKD-5 (Johansen et al., 2007; Bao et al., 2012; Roshanravan et al., 2013). Recent evidence suggests that frail HD patients are also more likely to experience a higher number of falls (McAdams-DeMarco et al., 2013).

Frailty is typically defined as a clinical phenotype consisting of low PA, gait speed, strength, unintentional weight loss, and exhaustion (Fried et al., 2001). All these components are intrinsically related to physical function, and they might represent risk factors for falls, not only when combined to assign a positive physical frailty score (McAdams-DeMarco et al., 2013), but also individually. In spite of the relatively high number of observational studies which consistently documented an increased risk of falling in dialysis populations (Desmet et al., 2005; Cook et al., 2006; Farragher et al., 2014), only a few studies explored the relationship between objective frailty/physical function measures and falls (Desmet et al., 2005; Cook et al., 2006; McAdams-DeMarco et al., 2013; Kutner et al., 2014; Wang et al., 2017; Kono et al., 2018), and reported contrasting results as to whether physical function is associated with falls in HD patients (paragraph 1.2.3.4, Chapter 1). The identification of which physical function/activity outcomes may be more closely associated with falls in people with CKD, if any, is of paramount importance, as this would eventually allow to develop new or tailor existing interventions that aim to reduce the occurrence of falls in CKD-5 patients on HD. One example of an evidence-based intervention that is effective in reducing symptoms associated with frailty such as falls in elderly, but otherwise healthy, individuals is strength and balance training exercise programmes (Sherrington et al., 2011). Therefore,

the main objective of this study was to perform a comprehensive assessment of frailty and physical function in a group of HD patients, and to explore the relationship with the risk of falling. The specific aims were to test the association between the Fried's frailty phenotype and falls, and to test the association between physical function and falls in a group of CKD-5 patients on HD. We hypothesised that 1) frailty would be positively associated with falling status and that, 2) physical function determinants, such as PA, upper and lower body strength, gait speed, TUG, CTSS-5 and postural balance would also be associated with falls.

4.2 Essential methods

4.2.1 Study design

A cross-sectional study design was used to explore the relationship between frailty, physical function, PA and falls in a group of prevalent CKD-5 patients on HD. The study participants underwent a comprehensive assessment of frailty and physical function measures at baseline, and they were subsequently classified as fallers or non-fallers based on the occurrence or not of at least one fall during a 12-month prospective observational period. In addition, patients with a history of at least one fall in the previous 12 months were also classified as fallers, so as to minimize the chances of misclassifying patients as non-fallers.

4.2.2 Data collection

Falls, frailty and physical function determinants such as PA levels, muscle strength, TUG, CSTS-5 and postural balance were assessed, as fully detailed in Chapter 2.

4.2.3 Sample size

Preliminary study size considerations are described in Chapter 2, paragraph 2.1.3.

The sample size (N) calculation was based on the smaller proportion (P1) of the dependent variable, as recommended in logistic regression analysis by Peduzzi et al., (1996), with the following formula: N= (10 K)/ P1. The dependent variable was defined as membership to the group "fallers" (≥ 1 fall sustained), and P1 was defined, based on the study results,

as P1= .389 (proportion of non-fallers, as reported in paragraph 4.3.3). “K” represents the number of independent (explanatory) variables, and equals to K= 2, as we entered 2 variables simultaneously in the model: the explanatory variable, e.g. frailty/physical function (one variable entered at a time) AND the diabetic status, which was retrospectively identified as a potential confounder of the study results. Therefore, substituting the values into the equation results in: N= (10* 2)/.389, which equates to N= 52. This is the minimum sample size required to provide an unbiased association for each explanatory variable in the logistic regression model (Peduzzi et al., 1996).

4.2.4 Statistical analysis

All statistical analyses were performed with SPSS (Version 23.0 for Windows, SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to check normality characteristics of data. Participants were classified and grouped as fallers and non-fallers. Between-groups differences in demographic, clinical characteristics, frailty status and physical function outcomes were assessed using a Chi-Square test for categorical variables, and by either Mann-Whitney U or independent t-tests, as appropriate, for continuous variables. Results are expressed as mean and standard deviation (SD) and percentages. Statistical limits for interpretation were set at an alpha level of $p = .05$. The association between frailty/physical function and falls (yes or no) was analysed by means of logistic regression analysis: variables reaching a statistical significance level of $p \leq 0.10$, in the preliminary independent comparisons, were entered in a univariate logistic regression model, which was adjusted a posteriori in a multivariate analysis.

In a sensitivity analysis, we also analysed the association between frailty/physical function and the number of falls recorded during the 12-month prospective follow-up by means of negative binomial regression analysis: variables reaching a statistical significance level of $p \leq 0.10$ in the univariate negative binomial regression model were entered in multivariate analysis. Statistical limits for interpretation of the logistic and negative binomial regression analyses were also set at an alpha level of $p = .05$.

4.3 Results

4.3.1 Participants

The screening and recruitment figures of the study are detailed in Chapter 3 (paragraph 3.3.1). Seventy-six patients were enrolled in the study and completed the baseline assessments. Nine patients were lost to follow-up, as detailed in paragraph 3.3.1, however five of these patients were retained in the data analysis due to their positive history of falls, which automatically classified these patients as fallers for the purposes of this cross-sectional investigation. All participants completed the physical function, strength and balance assessments, with the only exception of one patient (1.3%), who refused to undergo the balance and gait speed assessments. Moreover, two (2.6%) and five (6.6%) participants were removed from the TUG and CSTS-5 analysis respectively as they were unable to perform these tests as per protocol. In addition, 17 patients (22.4%) were excluded from the ActivPal data analysis, as they did not meet the minimum wearing time requirements described in Chapter 2, paragraph 2.4.1.2.

4.3.2 Demographic and clinical characteristics

Participants classified as fallers were more likely to have diabetes as primary renal disease (PRD) (34.9% vs 12.9%), and less likely to use diuretics (27.3% vs 53.3%) compared to non-fallers. No other differences were noted between the groups.

4.3.3 Falls

Forty-four patients out of the 72 included in the analysis (61.1%) reported at least 1 fall either in the previous 12 months, or during the 12-month follow-up period, and were therefore classified as “fallers”. The remaining 28 patients (38.9%) did not report any falls, and were classified as “non-fallers”. Further information on the falls estimates emerging from the study is detailed in Chapter 3, paragraph 3.3.3.

4.3.4 Frailty

Overall, 28 out of 76 patients (36.8%) were classified as frail. Fallers were more likely to be frail compared with non-fallers (Table 4.1). In addition, considering the single

components of frailty, fallers were also more likely to have low self-reported PA and more likely to meet the exhaustion criteria of frailty compared to non-fallers.

Table 4.1. Frailty characteristics of study participants: differences between fallers and non-fallers.

Variables	All patients (76)	Fallers (44)	Non-fallers (28)	P-value
Single frailty components				
Low PA (n) (%)	36 (47.2)	26 (59.1)	8 (28.6)	0.011
Low gait speed (n) (%)	22 (29.2)	16 (36.4)	5 (17.9)	0.092
Low strength (n) (%)	37 (48.6)	22 (50)	13 (46.4)	0.768
Exhaustion (n) (%)	57 (74.7)	37 (84.1)	17 (59.3)	0.020
Unintentional weight loss (n) (%)	13 (16.9)	9 (20.9)	3 (10.7)	0.262
Fried's frailty phenotype				
Frail (n) (%)	28 (36.8)	21 (47.7)	6 (21.4)	0.025

Abbreviations: PA: physical activity.

4.3.5 Physical activity

The differences between fallers and non-fallers in objective levels of PA are summarised in Table 4.2. Fallers had a significant lower count of daily steps, and lower time spent standing and stepping, compared with non-fallers.

Table 4.2. Objective measurements of PA: differences between fallers and non-fallers (mean ± SD).

Variables	All patients (72)	Fallers (44)	Non-fallers (28)	P-value
Time spent standing (h/day) (SD)	2.3 (1.1)	2.1 (1.1)	2.7 (1.2)	0.034
Time spent stepping (h/day) (SD)	0.7 (0.4)	0.6 (0.3)	0.8 (0.4)	0.016
Daily steps (n°) (SD)	3129 (1769)	2566 (1462)	3731 (1966)	0.015
Daily sit to stands (n°) (SD)	37.3 (12.2)	37.9 (13.8)	37.3 (10.7)	0.987

Abbreviations: SD: standard deviation; PA: physical activity.

4.3.6 Physical function performance

Physical function performance results are reported in Table 4.3. No significant differences between fallers and non-fallers were observed. As expected, handgrip strength was significantly higher in men compared to women (32.3±8.6 Kg vs 20.7±7 Kg, $p< 0.001$).

Table 4.3. Physical function performance tests: differences between fallers and non-fallers (mean ± SD).

Variables	All patients (72)	Fallers (44)	Non-fallers (28)	P-value
Strength				
Handgrip (Kg) (SD)	26.9 (9.8)	25.9 (9.6)	27.9 (8.9)	0.388
Leg extension (Kg) (SD)	19.8 (8.9)	19.1 (8.8)	21.5 (8.9)	0.259
Functional tests				
Gait speed (m/s) (SD)	0.86 (0.26)	0.81 (0.25)	0.93 (0.27)	0.060
TUG (s) (SD)	11.4 (4.9)	12.3 (5.6)	10.4 (3.7)	0.112
CSTS-5 (s) (SD)	17 (8.8)	17.7 (10)	16.2 (7)	0.789

Abbreviations: SD: standard deviation; TUG: timed up and go test; CSTS-5: 5 repetitions chair sit to stand test.

4.3.7 Postural balance

Compared to non-fallers, fallers had a significantly lower performance in seven (RangeY, RMSY, SP, AbsVel, VelX, VelY, and Area95) out of the nine balance variables in the EO condition, and in all nine variables in the EC condition (Table 4.4).

Table 4.4. Postural balance in EO and EC conditions: differences between fallers and non-fallers (mean ± SD).

	EO		EC	
Variables	**Fallers (44)**	**Non-fallers (28)**	**Fallers (44)**	**Non-fallers (28)**
RangeX (mm) (SD)	26.7 (15.7)	20.9 (6.6)	40.4 (20.6)*	28.1 (9.7)
RangeY (mm) (SD)	32.1 (16.7)*	24.1 (7.3)	46.8 (20.9)**	34.4 (10.8)
RMSX (mm) (SD)	5.4 (3.4)	4.2 (1.3)	7.3 (3.7)*	5.2 (1.8)
RMSY (mm) (SD)	6.3 (3.3)*	4.8 (1.6)	8.8 (4.8)*	6.5 (2.2)
SP (mm/s) (SD)	1081.3 (221.4)**	953.2 (200.7)	1329.1 (327)**	1124.2 (218.2)
AbsVel (mm/s) (SD)	43.3 (8.9)**	38.1 (8)	53.2 (13.1)**	45 (8.7)
VelX (mm/s) (SD)	27.2 (5.7)*	24.6 (5.7)	30.9 (6.6)**	27.1 (5.7)
VelY (mm/s) (SD)	27.8 (6)**	24 (4.8)	36.5 (11.2)**	30.1 (6.8)
Area95 (mm^2) (SD)	3218.2 (4252.8)*	1586.9 (947.8)	5778.5 (6831.7)*	2733.6 (1741.7)

Abbreviations: SD: standard deviation; EO: eyes open; EC: eyes closed; RangeX: range of centre of pressure (COP) displacement along the medial-lateral (ML) axis; RangeY: range of COP displacement along the anterior-posterior (AP) axis; RMSX: root mean square displacement along the ML axis; RMSY: root mean square displacement along the AP axis; SP: sway path; AbsVel: absolute velocity; VelX: velocity along the ML axis; VelY: velocity along the AP axis; Area95: 95% confidence ellipse area. * indicates a statistical significant difference between groups ($p < .05$); ** indicates a statistical significant difference between groups ($p < .01$).

4.3.8 Factors associated with falls

In univariate logistic regression, diabetic nephropathy, frailty, number of daily steps, and postural balance were associated with increased odds of falling (Table 4.5). In consideration of multicollinearity, and given the revealed high correlations among the different static postural balance variables (Appendix XIV), only one postural balance variable that had the strongest correlation (highest R^2) with falls, namely VelY in EO, was entered in the logistic regression model. The univariate analysis was adjusted for diabetic status, as we retrospectively identified this factor to be potentially a significant confounder of the study results. In the multivariate logistic regression model, frailty and postural balance were still significantly associated with increased odds of falling (Table 4.5).

Table 4.5. Logistic regression analysis: assessment outcomes associated with falls.

	Univariate		Adjusted	
Factors	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Clinical characteristics				
Diabetic nephropathy (yes/no)	3.616 (1.064–12.286)	0.039	-	-
Fried's frailty phenotype				
Frailty (yes/no)	3.348 (1.138-9.851)	0.028	3.153 (1.042-9.542)	0.042
Physical activity				
Time spent standing (h/day)	0.642 (0.387-1.066)	0.087	0.676 (0.401-1.139)	0.141
Daily steps (n°)	1.000 (0.999-1.000)	0.022	1.000 (0.999-1.000)	0.077
Physical function				
Gait speed (m/s)	0.160 (0.023-1.113)	0.064	0.161 (0.022-1.119)	0.074
Postural balance				
VelY in EO (mm/s)	1.149 (1.031-1.280)	0.012	1.140 (1.019-1.275)	0.022

Abbreviations: OR: odds ratio; CI: confidence interval; EO: eyes open; VelY: absolute velocity of centre of pressure (COP) along the anterior-posterior (AP) axis.

4.3.9 Sensitivity analyses

The results of the negative binomial regression analysis are summarised in Table 4.6. In univariate analysis, frailty, number of daily steps, number of daily sit-to-stands, handgrip strength, gait speed and TUG were associated with a higher number of falls. When this model was adjusted for diabetic nephropathy, only frailty, handgrip strength, gait speed and TUG remained significantly associated with falls.

Table 4.6. Sensitivity analyses. Negative binomial regression analysis.

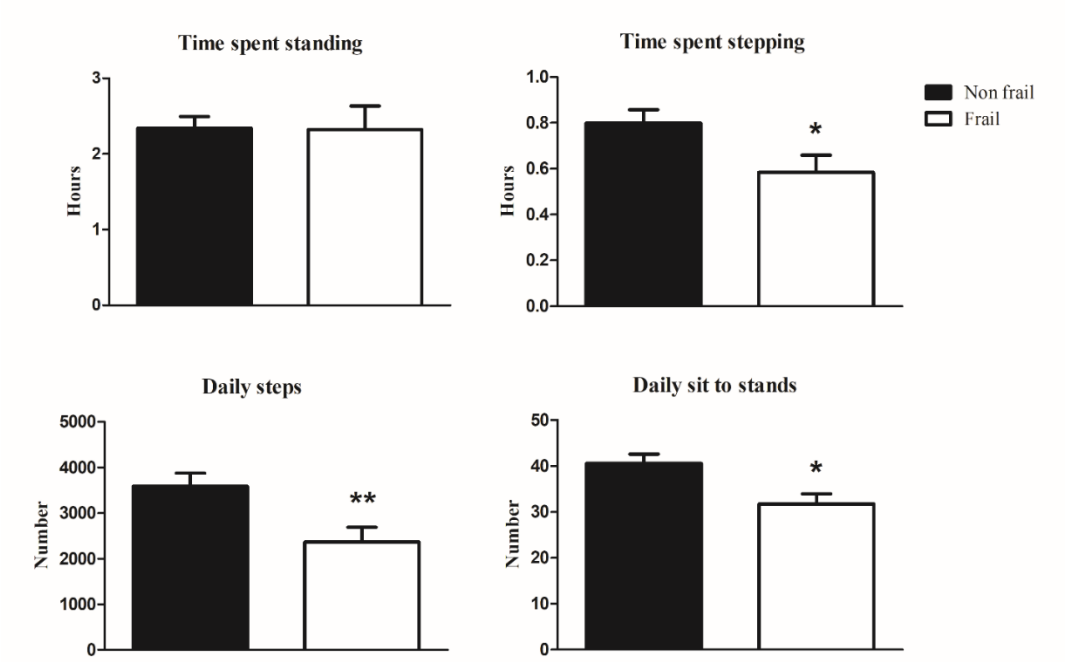
	Univariate		Adjusted*	
Factors	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
Clinical characteristics				
Diabetic nephropathy (yes/no)	3.00 (1.04-8.64)	0.042	-	-
Frailty & physical function				
Frailty (yes/no)	4.10 (1.60-10.51)	0.003	3.53 (1.39-8.94)	0.008
Time spent standing (h/day)	0.59 (0.32-1.08)	0.086	0.67 (0.37-1.20)	0.177
Daily steps (n°)	0.99 (0.99-1.00)	0.006	1.00 (0.99-1.00)	0.076
Daily sit to stands (n°)	0.96 (0.93-0.99)	0.042	0.98 (0.94-1.02)	0.384
Handgrip (Kg)	0.94 (0.88-0.99)	0.034	0.94 (0.89-0.99)	0.018
Gait speed (m/s)	0.08 (0.01-0.62)	0.016	0.11 (0.01-0.84)	0.034
TUG (s)	1.16 (1.02-1.32)	0.021	1.14 (1.00-1.29)	0.044
RangeY in EO (mm)	1.04 (0.99-1.10)	0.099	1.04 (0.99-1.09)	0.128

Abbreviations: RR: rate ratio; CI: confidence interval; TUG: timed up and go test; RangeY: range of COP displacement along the anterior-posterior (AP) axis: EO: eyes open. * This model was adjusted for diabetic nephropathy.

4.3.10 Further analyses

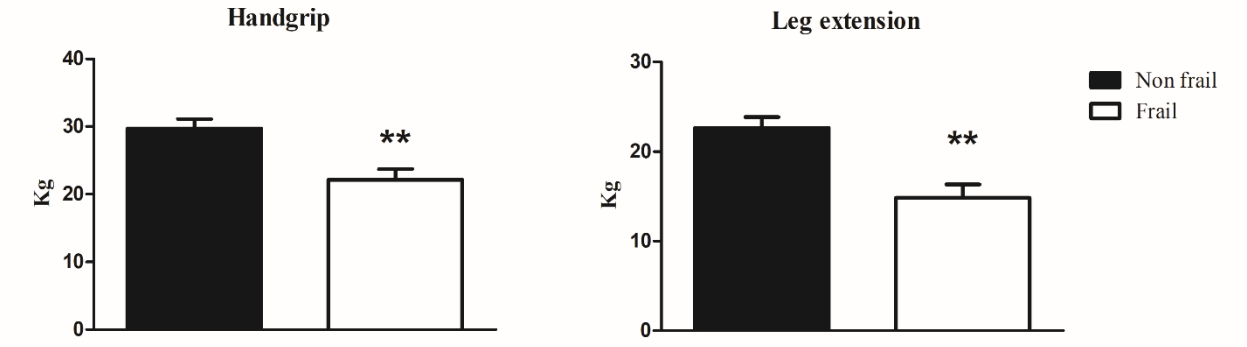
We also explored the differences in PA, strength, physical function tests, and postural balance between frail and non-frail patients, as an auxiliary analysis. The independent comparisons between these two groups revealed that all of these outcomes were markedly decreased in frail patients (Figures 4.1, 4.2, 4.3, 4.4).

Figure 4.1. Differences in PA between frail and non-frail patients (mean ± SEM)



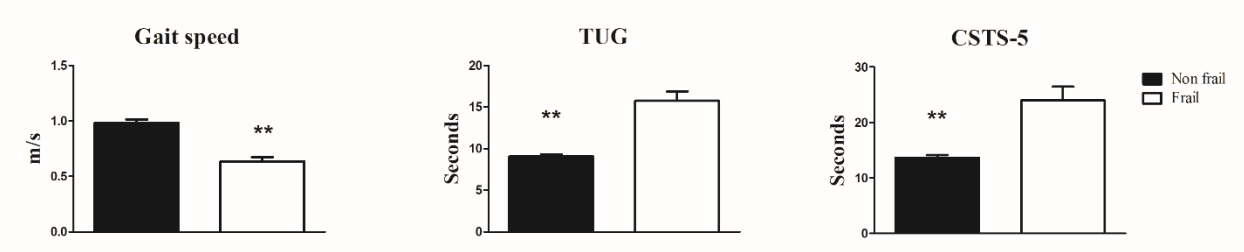
Abbreviations: SEM: standard error of the mean; PA: physical activity; * indicates a statistical significant difference between groups ($p < .05$); ** indicates a statistical significant difference between groups ($p < .01$).

Figure 4.2. Differences in strength between frail and non-frail patients (mean ± SEM)



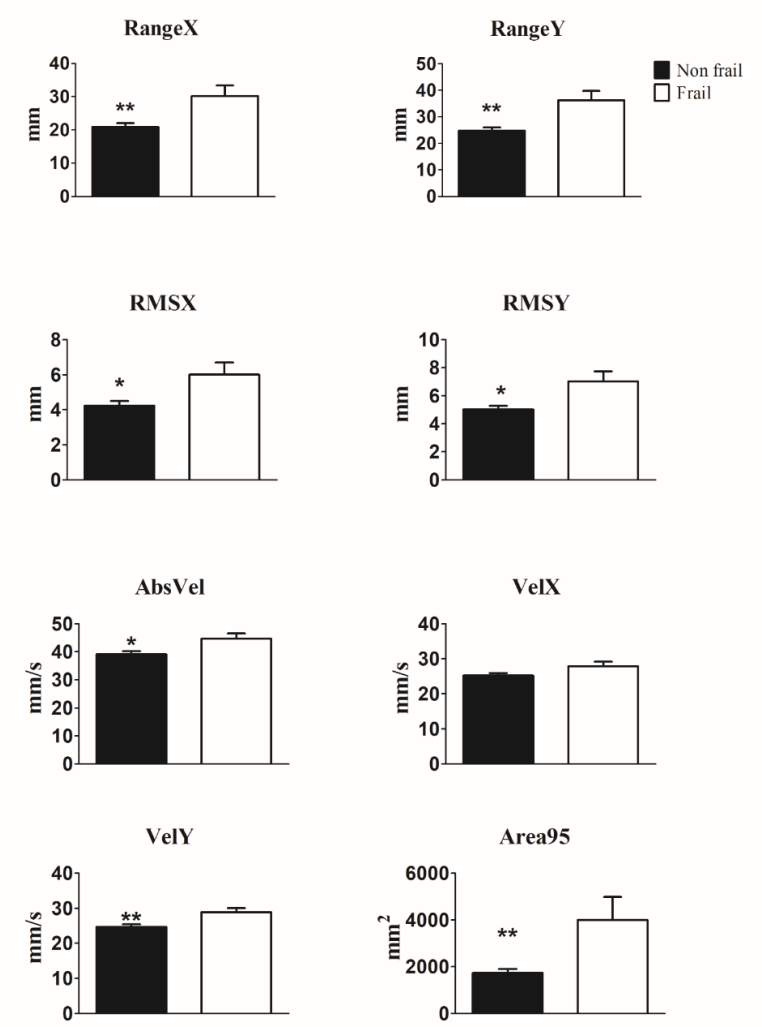
Abbreviations: SEM: standard error of the mean; * indicates a statistical significant difference between groups ($p < .05$); ** indicates a statistical significant difference between groups ($p < .01$).

Figure 4.3. Differences in functional tests. Frail vs non-frail patients (mean ± SEM)



Abbreviations: SEM: standard error of the mean; TUG: timed up and go test; CSTS-5: 5 repetitions chair sit to stand test; * indicates a statistical significant difference between groups ($p < .05$); ** indicates a statistical significant difference between groups ($p < .01$).

Figure 4.4. Differences in postural balance (EO). Frail vs non-frail patients (mean ± SEM)



Abbreviations: EO: eyes open; SEM: standard error of the mean; RangeX: range of centre of pressure (COP) displacement along the medial-lateral (ML) axis; RangeY: range of COP displacement along the anterior-posterior (AP) axis; RMSX: root mean square displacement along the ML axis; RMSY: root mean square displacement along the AP axis; AbsVel: absolute velocity; VelX: velocity along the ML axis; VelY: velocity along the AP axis; Area95: 95% confidence ellipse area; * indicates a statistical significant difference between groups ($p < .05$); ** indicates a statistical significant difference between groups ($p < .01$).

Additionally, we explored the relationships among PA, strength, physical function tests, and postural balance in the whole sample of study participants by means of Spearman's bivariate correlations. Overall, the PA variables did not correlate with postural balance in EO and strength. Time spent standing did not correlate to any of the physical function tests, while time spent stepping, number of daily steps, and number of daily sit to stands were moderately to strongly correlated with gait speed, TUG, and CSTS-5 ($.295 \leq R_s \leq .522$). Handgrip and leg extension strength were weakly to moderately ($-.234 \leq R_s \leq -.499$) correlated with the velocity-based measures of postural balance (AbsVel, VelX, and VelY) in both EO and EC conditions, and moderately to strongly correlated with physical function tests ($-.340 \leq R_s \leq -.508$). The physical function tests had weak to moderate correlations with postural balance ($-.232 \leq R_s \leq .500$). Lastly, three postural balance variables (RangeY, RMSY, Area95) in EC had weak to moderate correlations with time spent standing, time spent stepping, and number of daily steps ($-.259 \leq R_s \leq -.360$). The complete correlation tables of PA, strength, functional tests, and postural balance are summarised in the Appendices XV and XVI.

The relationship between diabetes and PA, strength, physical function tests, and postural control was also explored by means of Spearman's correlation (Tables 4.7 & 4.8). Diabetes as PRD did not correlate with physical function tests and postural balance. On the other hand, diabetes had a moderate negative correlation with time spent stepping and number of daily steps, as well as a moderate positive correlation with leg extension. Figure

4.5 displays the Venn's diagram summarising the distributions of falls, frailty, and diabetic status in the study population.

Table 4.7. Correlations of diabetes (PRD) and postural balance

Variables	RangeX in EO	RangeY in EO	RMSX in EO	RMSY in EO	AbsVel in EO	VelX in EO	VelY in EO	Area95 in EO
Diabetes (yes/no)	-0.068	0.088	-0.093	0.007	0.065	-0.053	0.125	-0.019
Sig.	0.566	0.453	0.431	0.950	0.583	0.653	0.287	0.871
	RangeX in EC	RangeY in EC	RMSX in EC	RMSY in EC	AbsVel in EC	VelX in EC	VelY in EC	Area95 in EC
	0.035	0.184	0.009	0.118	0.124	-0.016	0.183	0.065
Sig.	0.765	0.116	0.940	0.317	0.293	0.891	0.119	0.583

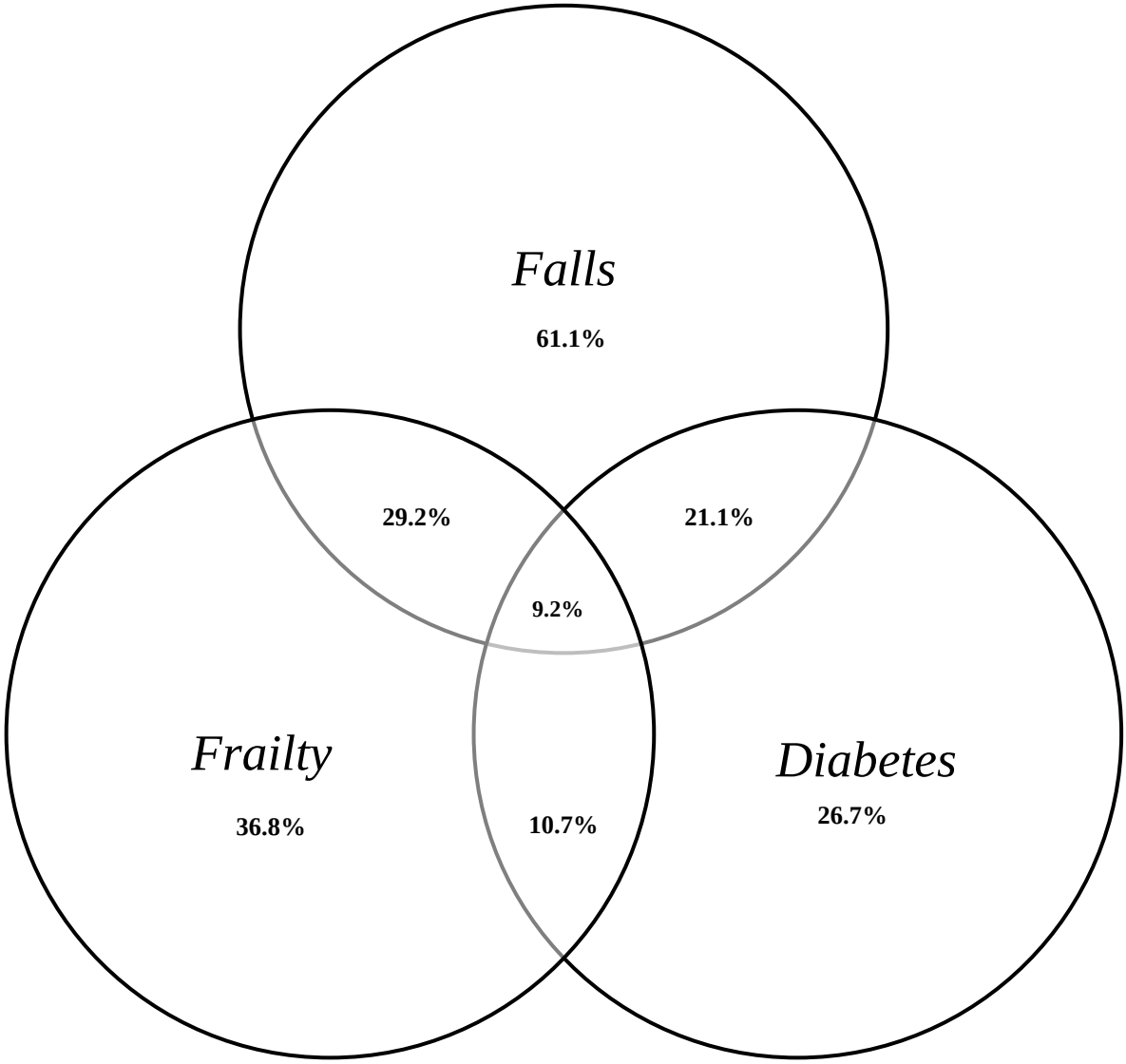
Abbreviations: PRD: primary renal disease; EO: eyes open; EC: eyes closed; RangeX: range of centre of pressure (COP) displacement along the medial-lateral (ML) axis; RangeY: range of COP displacement along the anterior-posterior (AP) axis; RMSX: root mean square displacement along the ML axis; RMSY: root mean square displacement along the AP axis; AbsVel: absolute velocity; VelX: velocity along the ML axis; VelY: velocity along the AP axis; Area95: 95% confidence ellipse area.

Table 4.8. Correlations of diabetes (PRD) and PA, strength, physical function

Variables	Time spent standing	Time spent stepping	Daily steps	Daily sit to stands	Handgrip	Leg extension	Gait speed	TUG	CSTS-5
Diabetes (yes/no)	-0.099	-.343	-.363	-0.204	0.067	.313	-0.075	0.085	-0.120
Sig.	0.454	0.008	0.005	0.122	0.566	0.006	0.524	0.473	0.324

Abbreviations: PRD: primary renal disease; PA: physical activity; TUG: timed up and go test; CSTS-5: 5 repetitions chair sit to stand test.

Figure 4.5. Venn's diagram: distribution of falls, frailty and diabetic status in the study population.



4.4 Discussion

We hypothesised that frailty and the falling status would be associated in CKD-5 patients on HD, and that physical function components such as PA, strength, TUG, CSTS-5 and postural balance would also be associated with falling.

The study findings seem to confirm the first research hypothesis, as the Fried's frailty phenotype, and its single components of self-reported exhaustion, and low PA levels were

significantly more prevalent in fallers compared to non-fallers. Moreover, frailty was associated with an approximately three-fold higher risk of falling in logistic regression analysis. As for the second research hypothesis, this appears to be at least partially supported as we found significant differences between fallers and non-fallers in postural balance, both in EO and EC condition, and in objectively measured PA variables, namely the number of daily steps and the time spent standing and stepping. Nevertheless, other physical function measures, such as the TUG, CSTS-5, handgrip, and leg extension did not differ significantly between the two groups. Moreover, only postural balance was associated with increased odds of falling in logistic regression analysis.

In agreement with a previous study, which reported frailty to be an independent predictor of a higher number of falls (McAdams-DeMarco et al., 2013), our study results also highlight a significant association of frailty with a positive falling status. Although McAdams-DeMarco et al., (2013) analysed the association between frailty and number of falls experienced, rather than the falling status (i.e. whether patients fell or not), the results from the two studies are remarkably similar, as highlighted by the odds ratios reported in the univariate (3.55, 95% CI: 1.68-7.46; vs 3.35, 95% CI: 1.14-9.85) and multivariate (3.09, 95% CI: 1.38-6.90; vs 3.15, 95% CI: 1.04-9.54) regression analysis, and they both suggest that frailty is associated with a roughly three-fold higher risk of falls in the CKD-5 population on HD. The single frailty components of self-reported exhaustion and low PA levels seemed to be the main drivers responsible for the positive association observed between frailty and falls, since these components were significantly more prevalent in fallers compared with non-fallers (84.1% vs 59.3%, and 59.1% vs 28.6% respectively). On the other hand, the unintentional weight loss, low strength and slow gait speed components were not significantly different in fallers and non-fallers, and consequently they may not contribute substantially to a higher risk of falls. Besides, the study results suggest that handgrip and leg extension strength were not significantly different between fallers and non-fallers, which further corroborates this observation. A more cautious interpretation should be made for the low gait speed component of frailty. Although the statistical analysis did not reveal a significant difference in this frailty component between the two groups, fallers tended to meet the Fried's criteria of low gait speed more frequently

than non-fallers (36.4% vs 17.9%, p= .092), and to have lower gait speed in absolute terms (0.81±0.25 m/s vs 0.93±0.27m/s, p= .06). Therefore, it should be acknowledged that this borderline statistical significance may be the result of the relatively small sample size of the study. Particularly, the small study size could have inflated the chances of committing a type II error, namely the probability of retaining a null hypothesis that is actually false.

Interestingly, both objective measurements of PA and strength had moderate to strong correlations with the physical function tests, in the whole sample of patients, but they did not correlate with each other. This observation seems to reflect the fact that low levels of PA and low strength are two independent components of frailty, and only the former seemed to be linked to an increased risk of falling. A study finding in support of this statement is that, additionally to the higher frequency of low self-reported PA in fallers compared to non-fallers, as highlighted by the Short IPAQ (Table 4.1), we also found lower objective measures of PA in the group of fallers (Table 4.2). The ActivPal results revealed that time spent standing and stepping, as well as the number of daily steps were significantly lower in fallers. Particularly, the average number of daily steps taken by the study participants (2566±1462 in fallers vs 3731±1966 in non-fallers) was considerably lower than the 7000-8000 steps/day threshold recommended to maintain a good physical fitness in elderly adults (Aoyagi et al., 2009). This was not surprising in light of the fact that dialysis patients have self-reported levels of PA below the 5^{th} percentile of healthy individuals (Johansen et al., 2010), and the association between low PA and falls, emerging from the study results, may ultimately reflect the effect of poor physical fitness on the occurrence of falls in this patient population.

Interestingly, we did not find any significant differences in physical function, as assessed by means of gait speed, TUG, and CSTS-5 in fallers vs non-fallers. These tests assess the physical function of the lower limbs in particular, which is strongly associated with all-cause mortality in CKD (Roshanravan et al., 2013). Despite the fact that both the TUG and the CSTS-5 have been suggested to be useful tools in predicting the probability of falls in older adults (Schumway-Cook et al., 2000; Ward et al., 2015), studies conducted in dialysis patients do not seem to confirm this relationship. Particularly, two studies examined, among other risk factors, the association between physical function and falls in

dialysis patients, and concluded that the TUG was not predictive of falls (Cook et al., 2006; Farragher et al., 2014), while other two studies (Desmet et al., 2005; Rossier et al., 2012) found significant differences in the arising test (the ability to rise from a chair without help from the arms) and in the performance-oriented mobility assessment (POMA) between fallers and non-fallers, in univariate but not in multivariate analysis.

Only one study reported failing to walk 10 meters unassisted as an independent predictor of falls in HD patients (Desmet et al., 2005). Although this kind of test assesses walking performance in a similar way to the 15 feet gait speed test, which was used in our study, the outcome of this assessment is a categorical binary variable (able/unable) as opposed to a continuous variable. The categorisation of walking performance in terms of able/unable to walk 10 meters independently implies arguably worse clinical outcomes compared to the low gait speed component of frailty (Chapter 2, paragraph 2.2.1) according to the Fried's criteria (Fried et al., 2001). Consequently, it is not surprising that the walking performance test administered by Desmet et al., (2005) resulted into a significant association with falls.

Ultimately, based on the study results and on the previous body of literature, it is not possible to pinpoint which, if any, physical function tests may be more closely associated with falling status in CKD-5 patients on HD. However, the observations that physical function, as assessed by the gait speed, TUG, and CSTS-5 tests, was the only component to correlate (moderately to strongly) with all the other physical function determinants, namely PA, strength and balance, and that frailty is intrinsically linked to lower physical function (Fried et al., 2001), seem to indirectly suggest that poor physical function may be inherently linked to falls, even if we didn't observe it in the current study. Further research is warranted to identify which tests may better predict falls in this patient population.

To the best of our knowledge, no previous research has explored the relationship between maximal isometric leg strength and falls, and our results did not reveal any significant association. Even though handgrip and isometric leg strength were markedly decreased in frail patients (Figure 4.2), as expected given that poor muscle strength is a defining component of frailty (Fried et al., 2001), we did not find any significant differences in

these variables between fallers and non-fallers. This finding suggests that, despite being closely related to frailty, muscle strength may not be a good predictor of falls in CKD-5 patients on HD.

The significant association between balance and falls is one of the most interesting findings of this investigation. Many significant differences in the postural balance variables emerged from the independent comparison of fallers and non-fallers, and most importantly postural balance (VelY in EO) was associated with increased odds of falling (OR: 1.14, 95% CI: 1.02-1.28, p= 0.022) in multivariate logistic regression analysis. Overall, patients with falls had statistically significant higher sway measures, indicating a worse balance performance and potentially a higher risk of falling (Maki et al., 1994). Particularly, seven and nine out of the nine variables taken for the analysis, in the EO and EC condition respectively, were significantly lower in fallers: this might indicate that static balance control is more closely associated with falls when vision is removed, a condition that highlights the importance of the proprioceptive regulatory component of balance (Horak et al., 1997). There are several possible explanations as to why proprioception might be impaired in CKD-5 patients undergoing HD. For instance, patients may present with peripheral neuropathy as a result of diabetes, uremia, or drug toxicity (Baluarte et al., 2017), while physical inactivity and low muscle mass could also hinder the proprioceptive integration processes. A further noteworthy finding was that postural balance (VelY in EO) resulted significantly associated with increased odds of falling even when the logistic regression analysis was adjusted for frailty status (OR: 1.12, 95% CI: 1.01-1.26, p= 0.04). This finding suggests that postural balance may be a risk factor for falls independent from frailty. Moreover, the observation that postural balance showed weak to moderate correlations with muscle strength and functional tests, but no correlation with PA, also indicates that postural balance represents a physical function outcome at least partially independent from frailty.

The prevalence of frailty in our study was 36.8%. Remarkably, a recent systematic review with meta-analysis concluded that the pooled prevalence of objectively measured frailty in CKD-5 patients is 36.8% (Kojima, 2017). Therefore, our findings are perfectly aligned with this estimate, and we are led to conclude that the study results relating to prevalence

of frailty may be generalised to the CKD-5 population. It should be highlighted that this prevalence is considerably lower than the 67-73% reported in larger observational studies that used a self-reported definition of frailty (Johansen et al., 2007; Bao et al. 2012), which further questions the validity of the frailty estimates obtained from these studies (Kojima et al., 2017). The prevalence of frailty emerging from our study is also fairly similar to the 41.8% found by McAdams-DeMarco et al., (2013), who also measured frailty objectively by means of the Fried's criteria (Fried et al., 2001). It should also be noted that the slightly smaller prevalence of frailty in our study, compared to McAdams-DeMarco et al., (2013), could be due to the stricter inclusion criteria. Because non-ambulatory patients, who are more likely to be frail, were not eligible to take part in the study, it is possible that this may have resulted in a slight underestimation of frailty in our cohort. Nevertheless, the prevalence of frailty was substantially higher than the 7% generally reported for the general population over 65 years of age (Fried et al., 2001), and we can conclude that our study results fully support the already overwhelming evidence that CKD-5 patients on HD are frailer than their non-uraemic, age-matched, counterparts (Kojima et al., 2017).

Interestingly, despite the self-evident relationship between age and frailty (Fried et al., 2001), age was not statistically different in fallers (59.9±13.2 years) compared to non-fallers (62.3±15.2 years). Although many studies reported age to be a significant risk factor for falls in dialysis patients (Desmet et al., 2005; Roberts et al., 2007; Rossier et al., 2012; Kutner et al., 2014; Farragher et al., 2014; Delgado et al., 2015; Kono et al., 2018), our finding is not an anomaly and is aligned with previous research that found no interaction between age and falls in HD patients (McAdams-DeMarco et al., 2013). Ultimately, in the context of CKD-5, the relationship between falls and age may be confounded by the presence of chronic inflammation, oxidative stress, and consequent muscle wasting, all of which contribute to a model of premature aging (Kooman et al., 2014).

As highlighted in paragraph 4.3.2, fallers were more likely to have diabetes as PRD compared to non-fallers (34.9% vs 12.9%). Although both diabetes and frailty were associated with falls, frailty was not significantly associated with diabetes, and when the logistic regression analysis was adjusted for diabetic status (Table 4.5) frailty was still

significantly associated with increased odds of falling (OR: 3.15, 95% CI: 1.04-9.54, p= 0.04). This finding seems to indicate that frailty is a risk factor for falls independent from diabetes. Moreover, diabetes did not correlate with most of the physical function measures (Tables 4.7 & 4.8) which further suggests that this factor may be linked to falls via a different aetiology in this patient group. The potential role of diabetes on falls will be further discussed in Chapter 5.

4.4.1 Study limitations

Because the study size was relatively small, we could not perform a more exhaustive a priori multivariate logistic regression analysis, which would be required to test more robustly the interrelationships between frailty, the physical performance outcomes, and falls.

In addition, the classification of fallers and non-fallers was based on self-reported information, which might be subjected to some degree of misreporting (Hauer et al., 2006). Although we sought to minimise the risk of underreporting falls by following up prospectively the participants every month (Cummings et al., 1988), patients were also classified as fallers if they recalled at least one fall in the previous 12 months and, since this is a longer recall interval, the potential for misreporting is higher (Ganz et al., 2005). It should be acknowledged that such a classification was made to counterbalance the risk of misclassifying patients with a significant, and fairly recent, history of falls as non-fallers just because they did not report any further falls during the prospective follow-ups.

4.4.2 Conclusions

In conclusion, this cross-sectional investigation indicates that frailty is associated with falls in CKD-5 patients undergoing HD therapy. Although frail patients had markedly decreased physical performance measures, such as lower PA, muscle strength, physical function, and postural balance, patients classified as fallers only showed lower levels of PA, and worse postural balance performance compared to non-fallers. Postural balance was also associated with increased odds of falling. This physical performance outcome is not traditionally included in the operational definition of frailty, and it might represent an

additional risk factor of falls. Further research is warranted to identify which physical function measures may be more closely associated with falls in the CKD-5 population on HD.

CHAPTER 5: BAROREFLEX FUNCTION, HAEMODYNAMIC RESPONSES TO AN ORTHOSTATIC CHALLENGE, AND FALLS IN HD PATIENTS

Abstract

Background: CKD-5 patients maintained on HD often present with dizziness and pre-syncopal events as a result of the combined effect of HD therapy and cardiovascular disease. The dysregulation of blood pressure (BP) during orthostasis may be implicated in the aetiology of falls in these patients. Therefore, we explored the relationship between baroreflex function, the haemodynamic responses to a passive orthostatic challenge, and falls in HD patients.

Methods: Seventy-six HD patients were enrolled in this cross-sectional study. Participants were classified as "fallers" and "non-fallers" and completed a passive head up tilting to 60º (HUT-60°) test on an automated tilt table. ECG signals, continuous and oscillometric BP measurements and impedance cardiography were recorded. The following variables were derived from these measurements: heart rate (HR) stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), number of baroreceptor events, and baroreceptor effectiveness index (BEI).

Results: The forty-four participants who were classified as fallers (57.9%) had a lower number of baroreceptor events (6.5±8.5 vs 14±16.7, p= .027) and BEI (20.8±24.2% vs 33.4±23.3%, p= .025). In addition, fallers experienced a significantly larger drop in systolic (-6.4±10.9 vs -0.4±7.7 mmHg, p= .011) and diastolic (-2.7±7.3 vs 1.8±6 mmHg, p= .027) oscillometric BP from supine to HUT-60° compared with non-fallers. None of the variables taken for the analysis were significantly associated with falls in multivariate logistic regression analysis.

Conclusions: This cross-sectional comparison indicates that, at rest, HD patients with a positive history of falls present with a lower count of baroreceptor sequences and BEI. Short-term BP regulation warrants further investigation as BP drops during a passive orthostatic challenge may be implicated in the aetiology of falls in HD.

5.1 Introduction

Cardiovascular disease is the most prevalent comorbidity in the CKD population (UKRR, 2016) and indices of poor cardiovascular function such as arterial stiffness (Wong et al., 2014), impaired BP responses to a passive orthostatic challenge (Shaw et al., 2015), and antihypertensive drug therapies (Tinetti et al., 2014; Angelousi et al., 2014), have been linked to a higher prevalence or incidence of falls in elderly but otherwise healthy individuals. In two prospective cohort studies, a lower pre-dialysis systolic BP was found to be associated with falling status in a group of elderly dialysis patients (Cook et al., 2006; Polinder-Bos et al., 2014) suggesting that falls might be mediated by low BP spells in these patients. Other researchers suggested that autonomic failure and the significant fluid shifts associated with HD therapy might place HD patients at an increased risk of postural dizziness and hypotensive symptoms, possibly resulting in falls (Roberts et al., 2003). In addition, Cook et al., (2006) reported that 31% of falls experienced by HD patients occurred during the transition from the seated to the upright position, suggesting that abnormal BP regulation, leading to dizziness spells, and potentially orthostatic hypotension, may be implicated in the aetiology of falls in these patients. All these observations lead us to hypothesise that impaired BP regulation particularly during postural changes may be an additional risk factor for falls that further exacerbates the risks coming from physical frailty and chronological aging alone.

The baroreceptor reflex, or baroreflex, is the main physiological mechanism involved in the short-lived haemodynamic responses to change in body position, by regulating BP, heart rate, cardiac output, peripheral resistance, and thus preventing hypotension (Schwartz et al., 2012). This mechanism may be altered in CKD patients, and its impairment has been linked to vascular stiffness, increased cardiovascular risk and all-cause mortality in CKD patients (Hildreth et al., 2012; Johansson et al., 2007). Despite the association of an impaired baroreflex control with the dysregulation of BP during orthostasis (Mattace-Raso et al., 2007), which could lead to hypotensive symptoms and falls, the relationship between baroreflex function and falls in HD patients has been largely unexplored. Therefore, our study is the first step in the process of collecting and documenting evidence of potential relationships between falls and BP control during an

orthostatic challenge in HD patients. We hypothesised that 1) lower baroreflex function would be associated with falling status, and that 2) self-reported fallers would be more likely to have worse haemodynamic responses to an orthostatic challenge.

5.2 Essential methods

5.2.1 Study design

A cross-sectional study design was used to explore the relationship between baroreflex/haemodynamic function and the falling status ("faller" vs "non-faller") in a group of prevalent CKD-5 patients on HD. The study participants underwent a comprehensive assessment of cardiovascular function measures at baseline, and they were subsequently classified as fallers or non-fallers based on the occurrence or not of at least one fall during a 12-month prospective observational period. In addition, patients with a history of at least one fall in the previous 12 months were also classified as fallers, so as to minimize the chances of misclassifying patients as non-fallers.

5.2.2 Data collection

Falls, baroreflex and haemodynamic function at rest, and in response to a passive orthostatic challenge consisting of HUT-60° were assessed, as fully detailed in Chapter 2.

5.2.3 Sample size

Preliminary study size considerations are described in Chapter 2, paragraph 2.1.3.

The sample size (N) calculation was based on the smaller proportion (P1) of the dependent variable, as recommended in logistic regression analysis by Peduzzi et al., (1996), with the following formula: N= (10 K)/ P1. The dependent variable was defined as membership to the group "fallers" (≥ 1 fall sustained), and P1 was defined, based on the study results, as P1= .389 (proportion of non-fallers, as reported in Chapter 4, paragraph 4.3.3). "K" represents the number of independent (explanatory) variables, and equals to K= 2, as we entered 2 variables simultaneously in the model: the explanatory variable, e.g. baroreflex/haemodynamic function (one variable entered at a time) AND the diabetic status, which was retrospectively identified as a potential confounder of the study results

(Chapter 4, paragraph 4.3.2). Therefore, substituting the values into the equation results in: N= (10* 2)/.389, which equates to N= 52. This is the minimum sample size required to provide an unbiased association for each explanatory variable in the logistic regression model (Peduzzi et al., 1996).

5.2.4 Statistical analysis

Statistical analyses were performed with SPSS (Version 23.0 for Windows, SPSS Inc., Chicago, IL). The Shapiro-Wilk Test (S-W) was used for the normal distribution checks of all data. Differences between fallers and non-fallers in demographic and clinical characteristics were analysed by means of a Chi-Squared test for categorical variables, and by either Mann-Whitney U or independent t-tests, as appropriate, for continuous variables: results are expressed as mean and standard deviation (SD). The effect of grouping, i.e. fallers vs non-fallers, on the baroreflex and haemodynamic variables was analysed by means of either parametric (independent t-tests) or non-parametric (Mann-Whitney U) independent comparisons, based on normal distribution assumptions. Statistical limits for interpretation were set at an alpha level of $p = .05$.

The association between the baroreflex function/haemodynamic responses and falls (yes or no) was analysed by means of logistic regression analysis: variables reaching a statistical significance level of $p \leq 0.10$, in the preliminary independent comparisons, were entered in a univariate logistic regression model, which was adjusted a posteriori in a multivariate analysis.

In a sensitivity analysis, we also analysed the association between cardiovascular function and the number of falls recorded during the 12-month prospective follow-up by means of negative binomial regression analysis: variables reaching a statistical significance level of $p \leq 0.10$ in the univariate negative binomial regression model were entered in multivariate analysis. Statistical limits for interpretation of the logistic and negative binomial regression analyses were also set at an alpha level of $p = .05$.

5.3 Results

5.3.1 Recruitment and loss to follow-up

The screening and recruitment figures of the study are detailed in Chapter 3 (paragraph 3.3.1). Seventy-six patients were enrolled in the study and completed the baseline assessments. As detailed in paragraph 3.3.1, nine patients were lost to follow-up. However, five of these patients were retained in the data analysis due to their positive history of falls, which automatically classified them as fallers for the purposes of this cross-sectional investigation. Moreover, 14 patients were excluded from the baroreflex function data analysis due to atrial fibrillation (n= 7; 9.2%) and to poor circulatory blood flow to the fingers, which rendered the contBP measurement unusable (n= 7; 9.2%). This resulted in the inclusion of 62 patients in the baroreflex function analysis. After the exclusion of the seven patients with poor blood circulation, 69 patients were retained for the haemodynamic responses analysis.

5.3.2 Demographic and clinical characteristics

Participants classified as fallers were more likely to have diabetes as primary renal disease (PRD) (34.9% vs 12.9%), and less likely to use diuretics (27.3% vs 53.3%) compared to non-fallers. No differences in other clinical characteristics were detected.

5.3.3 Falls

Forty-four and 28 patients were classified as fallers and non-fallers respectively, as detailed in Chapter 4 (paragraph 4.3.3). Further information on the falls estimates emerging from the study is detailed in Chapter 3, paragraph 3.3.3. The most commonly reported precipitating factors leading to a fall are synthesised in Chapter 3 (paragraph 3.3.4.3).

5.3.4 Haemodynamic and baroreflex function

The differences between fallers and non-fallers in all baroreflex variables are summarised in Table 5.1. At rest, fallers had a statistically significant lower count of baroreceptor “down-events” and “total-events”, which also resulted in a significant lower “down-BEI”

and “total-BEI”, compared to non-fallers. In addition, the “up-BEI” during HUT-60° was also significantly lower in fallers. No significant differences in BRS were detected between the two groups.

Table 5.1. Baroreflex function: differences between fallers and non-fallers (mean ± SD). Group means reflect averaged data for the total duration of five minutes in each postural position.

	Supine		**HUT-60**	
Variables	**Fallers (44)**	**Non-fallers (28)**	**Fallers (44)**	**Non-fallers (28)**
Up-ramps (n°) (SD)	20.6 (21)	19.5 (13.5)	23.2 (15.9)	17.8 (13.5)
Down-ramps (n°) (SD)	18.9 (17.7)	17.4 (11.9)	22.3 (14.2)	16.6 (12.9)
Total-ramps (n°) (SD)	39.5 (38.2)	36.8 (25)	45.5 (29.2)	34.5 (26)
Up-events (n°) (SD)	3.1 (4)	6.8 (9.5)	2.3 (3.5)	3.6 (4.4)
Down-events (n°) (SD)	3.4 (4.8)*****	7.1 (7.8)	3 (3.6)	3.9 (4.5)
Total-events (n°) (SD)	6.5 (8.5)*****	14 (16.7)	5.2 (6.3)	7.5 (8.4)
Up-BEI (%) (SD)	15.5 (20.1)	29.2 (29.4)	10.7 (13.6)*****	19 (15.7)
Down-BEI (%) (SD)	23.3 (27)*****	36.6 (22.8)	13.5 (15.7)	19.2 (15.7)
Total-BEI (%) (SD)	20.8 (24.2)*****	33.4 (23.3)	12.6 (13.4)	19.1 (13.2)
BRS (ms/mmHg) (SD)	9.2 (8.3)	10 (6.1)	6.8 (4.9)	9.8 (8.3)

Abbreviations: SD: standard deviation; HUT-60: head-up tilt at 60°; Up-BEI: up-events baroreceptor effectiveness index; Down-BEI: down-events baroreceptor effectiveness index; Total-BEI: total-events baroreceptor effectiveness index; BRS: baroreflex sensitivity; * indicates a statistical significant difference between groups ($p < .05$).

The haemodynamic variables of fallers and non-fallers, in the supine position and during HUT-60°, are described in Table 5.2. The differences in SV, CO, TPR, HR, contSBP, contDBP, OscSBP, and OscDBP from the supine position to HUT-60° are expressed as absolute values. A significant larger decrement of OscSBP and OscDBP from supine to HUT-60° was detected between fallers and non-fallers, while no differences in the remaining haemodynamic variables were found.

Table 5.2. Haemodynamic variables: differences between fallers and non-fallers (mean ± SD).

	Supine (1)		HUT60 (2)		Δ(1) - (2)	
	Fallers (44)	**Non-fallers(28)**	**Fallers (44)**	**Non-fallers (28)**	**Fallers (44)**	**Non-fallers(28)**
RRI (ms) (SD)	869.2 (134.1)	926.6 (187.5)	809.4 (168)	868.4 (192.8)	-57.9 (70.2)	-58.1 (64.5)
HR (bpm) (SD)	70.9 (10.7)	67.7 (13.2)	77.7 (15.2)	72.9 (15.2)	6.6 (8.3)	5.5 (5.8)
contSBP (mmHg) (SD)	125.4 (23.5)	122 (21.6)	126.6 (21.8)	125.1 (20.3)	3.5 (15.6)	3 (8)
contDBP (mmHg) (SD)	76.5 (14)	79.4 (16.4)	82 (15.2)	85.4 (16.3)	6.1 (10.2)	6 (7.6)
contmBP (mmHg)(SD)	97.3 (10.3)	97 (18.3)	100.8 (17.7)	101.9 (17.9)	4.7 (12.1)	4.9 (7.3)
SV (ml) (SD)	63.6 (14)	69.1 (16.1)	59.1 (11.8)	62.9 (15.5)	-4.1 (12.9)	-6.2 (16.3)
CO (L/min) (SD)	4.5 (1.1)	4.7 (1.5)	4.5 (0.9)	4.5 (1.2)	0.03 (0.9)	-0.2 (1.2)
TPR (dyne*s/cm^5)(SD)	1731.8 (432.4)	1763.9 (610.8)	1797.7 (451.5)	1919.5 (583.1)	77.9 (347.2)	155.5 (416.4)
SI (ml/m^2) (SD)	34.8 (8.3)	37 (10.7)	32.4 (7.4)	33.4 (8.5)	-2.2 (7)	-3.7 (9.1)
CI (L/min*m^2) (SD)	2.5 (0.7)	2.5 (1)	2.5 (0.5)	2.4 (0.7)	0.01 (0.5)	-0.1 (0.6)
TPRI(dyne*s*m^2/cm^5)	3168.5 (789.6)	3381.1 (1340.9)	3292.1 (807)	3645.1 (1260)	146.7 (624)	264.1 (773.5)
TFC (1/kOhm) (SD)	32.3 (10.6)	34.4 (11.1)	30.3 (10.1)	32.4 (11.1)	-1.6 (1.7)	-2 (1.8)
OscSBP (mmHg) (SD)	131.3 (22.6)	124.1 (19.8)	122.2 (18.3)	123.9 (13.1)	-6.4 (10.9)*****	-0.4 (7.7)
OscDBP (mmHg) (SD)	81.9 (12.9)	79.9 (15.8)	79.1 (13.2)	81.6 (17.4)	-2.7 (7.3)*****	1.8 (6)

Abbreviations: SD: standard deviation; HUT60: head-up tilt at 60°; RRI: R-R interval; HR: heart rate; contSBP: continuous systolic blood pressure; contDBP: continuous diastolic blood pressure; contmBP: continuous mean blood pressure; SV: stroke volume; CO: cardiac output; TPR: total peripheral resistance; SI: stroke index; CI: cardiax index; TPRI: total peripheral resistance index; TFC: thoracic fluid content; OscSBP: oscillometric systolic blood pressure; OscDBP: oscillometric diastolic blood pressure; Δ(1) - (2) represents the difference between the variables averaged over five minutes of HUT-60° and the variables averaged over five minutes of supine recording; * indicates a statistical significant difference between groups ($p < .05$).

5.3.5 Factors associated with falls

In univariate logistic regression, diabetic nephropathy, number of "down-events" and "total-events" in the supine position, "up-BEI" in the supine position, "up-BEI" in HUT-60°, OscSBP and OscDBP difference from the supine position to HUT-60° were associated with increased odds of falling (Table 5.3).

The univariate analysis was adjusted for diabetic status, as we retrospectively identified this factor to be potentially a significant confounder of the study results. In this multivariate logistic regression model, none of the variables were significantly associated with falling (Table 5.3).

Table 5.3. Logistic regression analysis: factors associated with falls.

	Univariate		Adjusted	
Factors	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Clinical characteristics				
Diabetic nephropathy (%)	3.616 (1.064–12.286)	0.039	-	-
Baroreflex function				
Down-events supine (n°)	0.909 (0.832-0.993)	0.034	0.932 (0.851-1.021)	0.130
Total-events supine (n°)	0.953 (0.910-0.997)	0.037	0.961 (0.919-1.006)	0.087
Up-BEI supine (%)	0.977 (0.956-0.999)	0.045	0.978 (0.954-1.001)	0.066
Up-BEI HUT-60 (%)	0.961 (0.925-1.000)	0.048	0.975 (0.936-1.015)	0.221
Down-BEI supine (%)	0.980 (0.959-1.001)	0.058	0.986 (0.964-1.008)	0.216
Total-BEI supine (%)	0.978 (0.956-1.001)	0.060	0.983 (0.960-1.008)	0.175
Total-BEI HUT-60 (%)	0.964 (0.925-1.005)	0.085	0.983 (0.940-1.027)	0.437
Haemodynamic variables				
OscSBP Δsupine – HUT60 (mmHg)	0.930 (0.871-0.992)	0.028	0.939 (0.876-1.008)	0.080
OscDBP Δsupine – HUT60 (mmHg)	0.894 (0.813-0.983)	0.021	0.908 (0.816-1.010)	0.075

Abbreviations: CI: confidence interval; Up-BEI: up-events baroreceptor effectiveness index; Down-BEI: down-events baroreceptor effectiveness index; Total-BEI: total-events baroreceptor effectiveness index; HUT60: head-up tilt at 60°; OscSBP: oscillometric systolic blood pressure; OscDBP: oscillometric diastolic blood pressure; ΔSupine-HUT60 represents the difference between the variables averaged over five minutes of HUT-60° and the variables averaged over five minutes of supine recording.

5.3.6 Sensitivity analyses

The results of the negative binomial regression analysis are summarised in Table 5.4. In univariate analysis, baroreflex indices of frequency such as number of up-events, number of down-events, number of total-events, up-BEI, down-BEI and total-BEI in the supine position were associated with a higher number of falls. In addition, the CO and OscDBP

responses to HUT-60° were also associated with a higher number of falls. When the univariate model was adjusted for diabetic nephropathy, all baroreflex measures remained significantly associated with falls, while only the CO response to HUT-60° remained significantly associated.

Table 5.4. Sensitivity analyses. Negative binomial regression analysis.

	Univariate		Adjusted*	
Factors	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
Clinical characteristics				
Diabetic nephropathy (yes/no)	3.00 (1.04-8.64)	0.042	-	-
Cardiovascular function				
Up-events supine (n°)	0.83 (0.72-0.96)	0.010	0.86 (0.75-0.99)	0.032
Down-events supine (n°)	0.86 (0.76-0.96)	0.009	0.88 (0.78-0.99)	0.042
Total-events supine (n°)	0.91 (0.86-0.98)	0.008	0.93 (0.87-0.99)	0.029
Up-BEI supine (%)	0.96 (0.94-0.99)	0.004	0.97 (0.95-0.99)	0.015
Down-BEI supine (%)	0.96 (0.94-0.98)	0.001	0.97 (0.95-0.99)	0.005
Total-BEI supine (%)	0.96 (0.93-0.98)	<0.001	0.96 (0.94-0.99)	0.003
RRI Δsupine – HUT60 (mmHg)	1.01 (0.99-1.02)	0.074	1.00 (0.99-1.01)	0.714
CO Δsupine – HUT60 (L/min)	0.51 (0.27-0.98)	0.043	0.55 (0.31-0.98)	0.043
CI Δsupine – HUT60 (L/min*m^2)	0.32 (0.10-1.06)	0.063	0.40 (0.15-1.05)	0.061
OscSBP Δsupine – HUT60 (mmHg)	0.95 (0.89-1.01)	0.084	0.98 (0.92-1.04)	0.507
OscDBP Δsupine – HUT60 (mmHg)	0.90 (0.83-0.98)	0.010	0.95 (0.86-1.04)	0.240

Abbreviations: RR: rate ratio; CI: confidence interval; Up-BEI: up-events baroreceptor effectiveness index; Down-BEI: down-events baroreceptor effectiveness index; Total-BEI: total-events baroreceptor effectiveness index; CO: cardiac output; RRI: R-R interval; CI: cardiac index; OscSBP: oscillometric systolic blood pressure; OscDBP: oscillometric diastolic blood pressure; Δsupine-HUT60 represents the difference between the variables averaged over five minutes of HUT-60° and the variables averaged over five minutes of supine recording. * This model was adjusted for diabetic nephropathy.

5.3.7 Further analyses

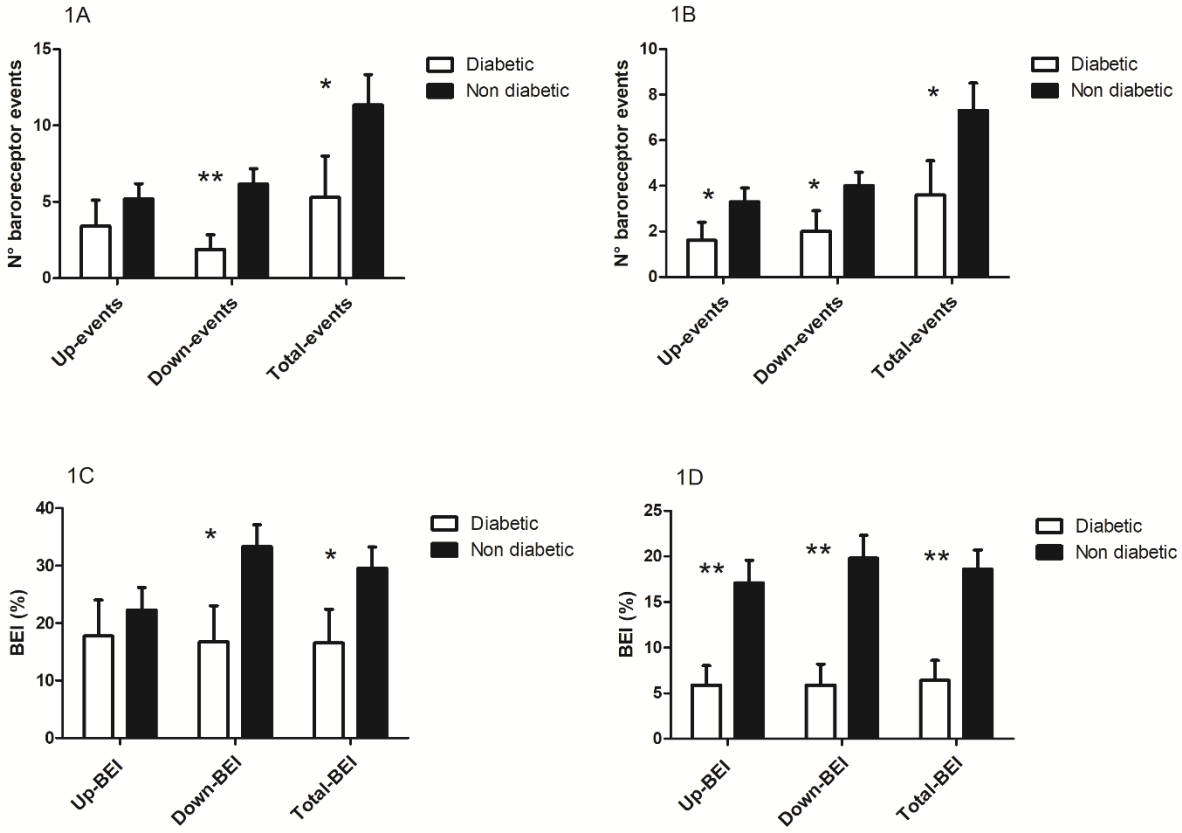
In order to evaluate the weight of the confounding effect of diabetes on the study results, we compared diabetic vs non-diabetic patients in terms of baroreflex function and BP

response to HUT-60°. The independent comparisons between the two groups indicate that these variables were markedly decreased in diabetic patients (Figure 5.1 & 5.2).

In addition, we also performed a point biserial correlation analysis in the sub-group of non-diabetic patients (N=44) to explore the relationship between the factors entered in logistic regression analysis and falls. No significant correlations were found for any of the baroreflex function/haemodynamic variables and falls ($-0.223 \leq R_s \leq -0.088$; $0.151 \leq$ P-values≤ 0.583) when diabetic patients were removed.

The heart rate variability (HRV) characteristics of the study participants are also summarised in the appendix XVII.

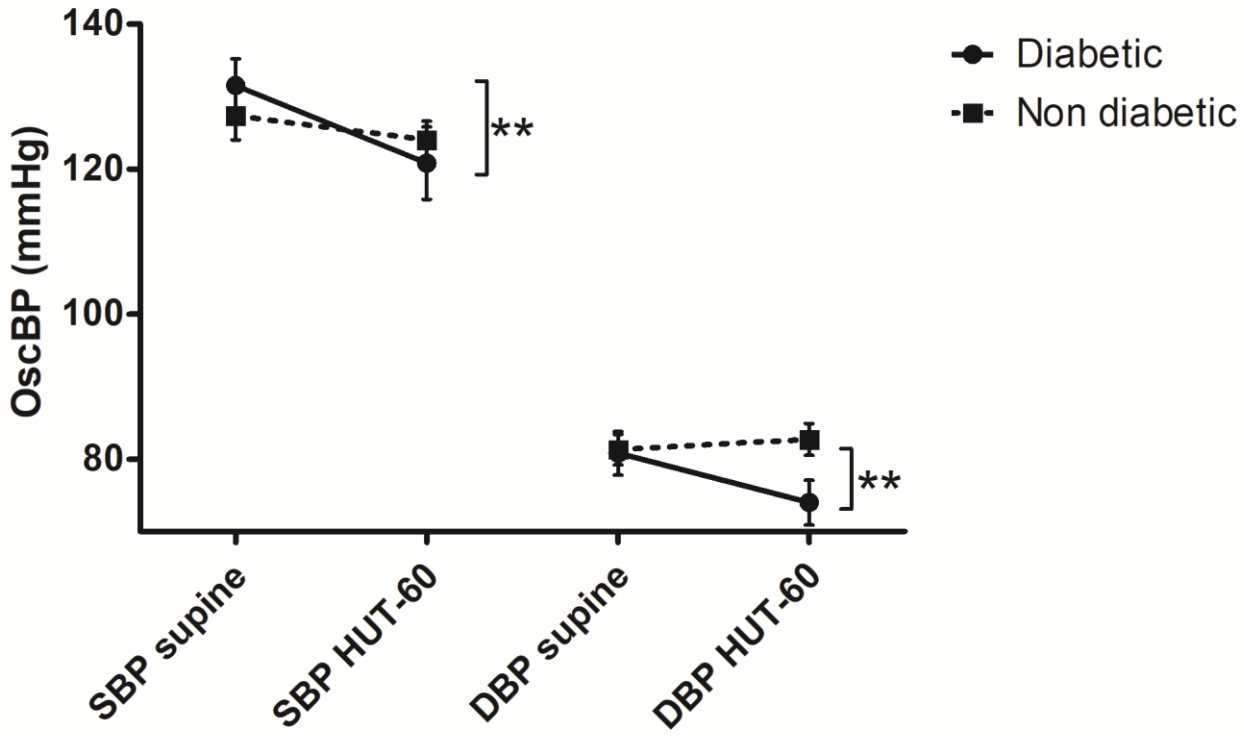
Figure 5.1. Baroreflex function in diabetic vs non-diabetic patients.



Abbreviations: BEI: baroreceptor effectiveness index. Figure 1A shows the number of baroreceptor events in the supine position; Figure 1B shows the number of baroreceptor events in HUT-60°; Figure 1C shows the BEI measured in the supine position; Figure 1D

shows the BEI measured in HUT-60°. * indicates a statistically significant difference (p< .05). ** indicates a statistically significant difference (p< .01).

Figure 5.2. Changes in BP during transition from the supine position to HUT-60° (diabetic vs non diabetic).



Abbreviations: OscBP: oscillometric blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; ** indicates the statistically significant drop in OscBP in diabetic patients (p< .01).

5.4 Discussion

We hypothesised that HD patients classified as fallers would have worse baroreflex function than patients free from falls. In addition, we hypothesised that patients with falls would have worse haemodynamic responses to an orthostatic challenge.

We found that at rest, fallers had lower counts of baroreceptor "down-events" and "total-events", as well as a lower down-BEI and total-BEI compared to non-fallers. Although

we also expected to see a significantly impaired ability to effectively regulate the haemodynamic variables via the arterial baroreflex mechanism in the fallers group, in response to a passive orthostatic challenge, this was not confirmed. However, we noted a significantly larger drop in OscBP during the transition from supine to HUT-60^{o} which warrants further investigation.

Our findings on baroreflex function suggest that a lower number of baroreceptor sequences might discriminate patients with falls from those who are falls-free. Although no differences in the baroreflex slope, as assessed by BRS, were detected between fallers and non-fallers, measures reflecting how often the baroreflex is activated, such as the number of "down-events" and the "total-events", among other BEI indices, were significantly lower in the group of fallers. Interestingly, in resting conditions, the baroreceptor down-regulation seemed to better discriminate fallers from non-fallers. A baroreceptor down-event occurs when a systolic BP drop is coupled with a concomitant decrease of the RRI, namely an increase in HR. This is a physiologic response to a spontaneous perturbation of BP, which allows the maintenance of haemodynamic homeostasis (Schwartz et al., 2012). Therefore, the lower count of baroreceptor "down-events" observed in fallers, as well as the lower "down-BEI" might indicate a relationship between the failure to increase HR in response to a spontaneous drop in BP and falls.

It should also be noted that, even though we did not assess a control group of healthy participants, the BEI indices measured in our patients (20.8±24.2% in fallers, and 33.4±23.3% in non-fallers) are considerably lower than the average 58±20% BEI measured in healthy individuals (Pitzalis et al., 2003), while their BRS values were only slightly inferior (-15% to -25%) to those of an age-matched healthy population (Tang et al., 2014). Because a reduced BEI has already been shown to be an independent predictor of all-cause mortality in patients with CKD (Johansson et al., 2007), it is possible that this index might predict other adverse outcomes such as falls in this population. Potentially, the lower BEI as well as the lower number of baroreceptor events could be linked to syncope-related falls due to an impaired homeostasis of the HR and BP responses, which may lead to cerebral hypoperfusion with sudden onset of dizziness and pre-syncopal symptoms, which are commonplace among HD patients (Roberts et al., 2003).

Interestingly, in the current study, almost half of the patients who experienced falls during the prospective observational follow-ups (46.2%) reported dizziness or syncope-like events as one of the symptoms preceding a falling event, which indirectly implicates this mechanism in the aetiology of falls in HD patients.

Although a direct biologic mechanism may exist between baroreflex function and falls, given the relationship between impaired baroreflex function and orthostatic BP decrements (Mattace-Raso et al., 2007), the study results do not seem to fully support the hypothesis that poor baroreflex function and orthostatic BP regulation are independent risk factors for falls in HD patients. While several baroreflex indices, as well as OscBP, were associated with falls in univariate logistic regression, adjusting the model for diabetic status resulted in no significant association between the baroreflex function/haemodynamic responses and falls.

The role of diabetes, in the context of our study, plays a crucial role as 34.9% of the patients classified as fallers had diabetic nephropathy as PRD, compared to only 12.9% in the group of non-fallers. Diabetic nephropathy represents an advanced stage of diabetes, which is commonly associated with cardiovascular autonomic neuropathy and chronic sympathetic over-activity, both of which can affect the baroreflex and potentially the haemodynamic responses to orthostasis (Fisher et al., 2017). Therefore, the higher proportion of diabetic patients amongst fallers is likely to be a main driver of the significant differences observed between fallers and non-fallers in terms of baroreflex function and BP response to orthostasis.

The point biserial correlation analysis performed in the subgroup of non-diabetic patients did not reveal any significant correlations between any of the baroreflex/haemodynamic variables and falls, which highlights the mediating effect of diabetes on the study results. This is an interesting finding considering that diabetes has been found to be an independent risk factor for falls in HD patients (Desmet et al., 2005), and our study results seem to indirectly suggest that impaired baroreflex and BP dysregulation may be one of the biological mechanisms underlying the higher occurrence of falls amongst diabetic HD patients.

Surprisingly, we did not find any differences in the SV, CO, TPR, HR, contSBP, and contDBP responses to the HUT-60° between fallers and non-fallers. This lack of effect may be explained in light of the relatively short duration of the orthostatic challenge. Although five minutes of orthostasis are considered to be sufficient for the diagnosis of orthostatic hypotension, according to the current guidelines (Brignole et al., 2004), it is possible that a longer orthostatic challenge could have yielded different results. For instance, Shaw et al., (2015) examined the cardiovascular responses to orthostasis in a group of elderly residents in long-term facilities. They found that, during an orthostatic challenge, the decreases in contBP were larger in those with a history of falls, but only in the delayed phase of orthostasis (3-15 minutes) rather than at the initial phase (0-3 minutes). This might explain why we found a significant larger decrement in OscBP, but not in contBP between fallers and non-fallers: whilst OscBP assessment consists of single measurements, which capture the BP at a single time-frame, contBP may provide more useful information than single sphygmomanometer assessments, in terms of actual beat-to-beat variations of BP (Pasma et al., 2014), but its measurement represents an average of several measurements over a given interval of interest. Therefore, the two type of BP measurements, despite being performed in the same phases, do not represent exactly the same haemodynamic data.

During HUT-60°, for instance, the contSBP and contDBP reflect the overall BP performance over the five minutes of data acquisition and it is possible that a longer recording interval may also have revealed a larger decrement of BP in fallers. Moreover, the discrepancy between contBP and OscBP measurements during HUT-60° could also be explained in light of a possible hydrostatic effect: because postural changes can modify the distribution of hydrostatic pressures in fluid-filled body compartments (Hinghofer-Szalkay, 2011), it is possible that the transition from supine to HUT-60° may have influenced to some extent the response of contBP due to the initial gravitational shift. On the other hand, during HUT-60°, OscBP was measured when the patient was already in the upright position, and therefore this measurement would be less subjected to hydrostatic adjustments arising from the tilting procedure. Although we sought to minimise the hydrostatic effects of tilting by standardising the testing procedures, as described in

appendix IX, it is possible that these may have played a role in the discrepancy observed between the two kinds of BP assessments.

It should also be acknowledged that the resting BP of the study participants was surprisingly low considering that HD patients are usually hypertensive. This relatively low BP may be explained in light of the strict testing standardisation procedures which were designed to ensure the best possible haemodynamic state balance (e.g. no caffeine, supine rest prior to the assessment, non-dialysis day), and also by a possible underestimation of BP from the Task Force® Monitor (Brittain et al., 2018). Although this should not affect the study results, since the research aim was focused on exploring the relationship between the relative change in BP and falls, rather than the absolute values of BP, the generalisability of the study results to patients with higher or more poorly controlled resting BP should be cautious.

Only a few studies examined the BP changes in response to orthostasis in HD patients, and found no association between the BP response to a pre-dialysis (Cook et al., 2006) or post-dialysis (Desmet et al., 2005; Roberts et al., 2007) orthostatic assessment and the patients' falling status. Nevertheless, these studies assessed the BP response by means of OscBP measurements after active standing, a procedure that may be subjected to standardisation issues compared to the head-up tilt test, which is considered the reference standard for the assessment of orthostatic hypotension (Cooke et al., 2009). In addition, it should be acknowledged that the tilting angle might also be partly responsible for the lack of response. Typically, angles of 60°-90° are widely implemented in clinical practice (Khurana et al., 1996) and thus tilting patients beyond 60° could have constituted a larger haemodynamic challenge and concomitant response.

The incidence of falls recorded was 1.16 falls/patient-year and is approximately 2.3 times greater than seen in the non-uraemic, community-dwelling elderly (O'Loughlin et al., 1993). This confirms the increased risk of falling of HD patients compared with the general healthy population (Desmet et al., 2005). Although the current study was conducted in a small cohort of patients, our findings relating to the incidence of falls are broadly in agreement with those of larger observational studies. In particular, Desmet et al., (Desmet et al., 2005), reported a yearly incidence of 1.18 falls/patient-year for their

HD patients, which is very similar to that observed in our study (1.16 falls/patient-year). Additionally, the proportion of patients observed in our study, who experienced at least one fall during the 12-month follow-up (37.7%), is also very similar to that reported in previous research (28.3%) (McAdams-DeMarco et al., 2013). Therefore, our findings on falling behaviour in HD patients seem to be representative of this patient group, and results from this study may be generalised to the general population of CKD-5 patients undergoing HD therapy.

5.4.1 Study limitations

First of all, the classification of patients in fallers and non-fallers was based on self-reported information. As previous research has highlighted how recalling information about falls might be subjected to misreporting (Hauer et al., 2006), this could have resulted in some degree of misclassification in the group allocation. We sought to minimise this bias by following up prospectively the participants every month (Cummings et al., 1988), although patients were also classified as fallers if they had experienced at least one fall in the previous 12 months: this kind of information is theoretically more susceptible to misreporting given the longer recall interval (Ganz et al., 2005). The decision to classify the patients with a previous history of falls also as fallers, regardless of the occurrence of any new fall event during the observational follow-up, was made to counterbalance another risk of bias, namely that of blindly assuming that all patients were free from the clinical outcome of interest, i.e. falls, at the beginning of the study.

In addition, the relatively small sample size did not allow the application of a more exhaustive, a priori, multivariate logistic regression analysis to more robustly test the interrelationships between baroreflex function, haemodynamic responses, and falls.

5.4.2 Conclusions

This study indicates that, at rest, HD patients classed as “fallers” present with worse baroreflex indices reflecting how often the baroreflex is activated, as highlighted by the lower number of baroreceptor-mediated sequences of coupled HR and BP. Additionally, a significantly larger decrement of OscBP was observed in “fallers”, even though other

haemodynamic responses to HUT-60° were not seen to differ between fallers and non-fallers. Patients with falls were also more likely to have diabetes as PRD, and the diabetic status seems to at least partly mediate the relationship between baroreflex function/BP responses to orthostasis and falls. The short-term BP regulation warrants further investigation as BP drops during the transition from supine to an upright position may be implicated in the aetiology of falls in HD.

CHAPTER 6: THE RELATIVE IMPORTANCE OF FRAILTY, PHYSICAL AND CARDIOVASCULAR FUNCTION AS PREDICTORS OF FALLS IN CKD-5 PATIENTS ON HD

Abstract

Background: The population of CKD-5 patients on HD is at greater risk of falling compared to non-uraemic individuals living in the community. Previous research has suggested that frailty may be the primary contributor to the increased risk of falling in this clinical population. However, HD patients often present with abnormalities of cardiovascular function such as baroreflex impairment and orthostatic dysregulation of BP which may also be implicated in the aetiology of falling. Therefore, we aimed to explore the relative importance of frailty and cardiovascular function as potential exercise-modifiable predictors of falls in these patients.

Methods: A convenience sample of prevalent CKD-5 patients on HD was enrolled in this prospective study. Participants completed a comprehensive assessment of frailty, physical and cardiovascular function as detailed in Chapters 4 and 5 (paragraphs 4.2 and 5.2), and the number of falls experienced during a 12-month observational follow-up was recorded. Sixty-nine participants completed the observational follow-ups and were included in the data analysis of this Chapter. The association between the potential frailty and cardiovascular predictors of falls and the number of falls documented during follow-up was analysed by means of negative binomial regression modelling. Sensitivity analyses by means of receiver operating characteristics (ROC) curve analysis were also performed. Statistical limits for interpretation were set at an alpha level of $p = .05$.

Results: In multivariate analysis, only worse baroreflex function, as assessed by means of total-BEI (RR: 0.96, 95%CI: 0.94-0.99, p= 0.004), and orthostatic decrements of OscDBP to HUT-60° (RR: 0.93, 95%CI: 0.87-0.99, p= 0.033) were associated with a greater number of falls. In ROC curve analysis, frailty alone did not discriminate significantly fallers from non-fallers, while adding the cardiovascular index total-BEI resulted in a significant 6% improvement of the area under the curve (AUC).

Conclusions: This prospective study indicates that cardiovascular mechanisms implicated in the short-term regulation of BP showed a greater relative importance than frailty in predicting falls in CKD-5 patients on HD. These findings challenge the current assumption that frailty is the primary factor in the aetiology of falling in this clinical population.

6.1 Introduction

Falls, and fall-related injuries may be one of the most frequently observed frailty-related adverse outcomes in the population of CKD patients (Lopez-Soto et al., 2015). Consequently, a few observational studies conducted in CKD-5 patients on HD have recently explored the relationship between frailty and falls in this patient group, and they all concluded that, not surprisingly, these are significantly associated (McAdams-DeMarco et al., 2013; Kutner et al., 2014; Delgado et al., 2015). Moreover, the study findings reported in Chapter 4 of this PhD thesis (paragraphs 4.3.4 and 4.3.8) further corroborate the observation that frail HD patients have increased odds of falling compared to those who are not frail.

Along with frailty, CVD is also highly prevalent in CKD-5 patients and impaired cardiovascular function is associated with multiple adverse clinical outcomes (Foley et al., 1997). A few studies have also begun to better explore the link between clinical outcomes such as falls and cardiovascular dysregulation in this patient group (Roberts et al., 2003; Roberts et al., 2007). In particular, it appears that the CKD-5 population on dialysis may be at risk of hypotension that can lead to postural dizziness, and potentially falls. This is further exacerbated by the combined effect of autonomic failure and the significant fluid shifts associated with dialysis (Roberts et al., 2003). In Chapter 5 of this PhD thesis (paragraph 5.3.4), we highlighted a significant larger drop of BP, in response to a passive orthostatic challenge, in patients with falls compared to those who were falls-free. Moreover, this orthostatic decrement in BP, as well as worse indices of baroreflex function, were also significantly associated with falls in univariate logistic regression analysis (paragraph 5.3.5). All of these observations seem to indirectly suggest that impaired BP control, to maintain haemodynamic stability, might be implicated as an

additional factor in the aetiology of falls in the CKD-5 population on dialysis, due to the CKD-related autonomic failure and/or the dialysis-related hypotension. From a rehabilitation/therapeutic perspective, this could have important translational impact, since the short-term regulation of BP, as assessed by means of baroreflex function, has been shown to improve following active interventions such as exercise (Petraki et al., 2008). The objective of this investigation was to explore the relative importance of frailty and cardiovascular function as potential exercise-modifiable predictors of falls in CKD-5 patients on HD. We hypothesised that 1) frailty and cardiovascular function would be associated with a higher number of falls, and that 2) modelling the risk of falling by adding a cardiovascular function variable to frailty would improve the prediction of falls sustained and recorded over a 12-month period in CKD-5 patients on HD.

6.2 Essential methods

6.2.1 Study design

An observational prospective cohort study design was used to investigate the association between potential predictors of falls (e.g. frailty, cardiovascular function) and the number of falls sustained over a 12-month follow-up period in CKD-5 patients on HD.

6.2.2 Data collection

Falls, frailty, physical function determinants (PA levels, muscle strength, TUG, CSTS-5, postural balance), baroreflex and haemodynamic function at rest, and in response to a passive orthostatic challenge consisting of HUT-60° were assessed, as fully detailed in Chapter 2.

6.2.3 Statistical analysis

Statistical analyses were performed with SPSS (Version 23.0 for Windows, SPSS Inc., Chicago, IL). The Shapiro-Wilk Test (S-W) was used to assess whether data were normally distributed. Differences between fallers and non-fallers in demographic, clinical, frailty, and cardiovascular characteristics were analysed by means of a Chi-Squared test

for categorical variables, and by either Mann-Whitney U or independent t-tests, as appropriate, for continuous variables.

The association between baseline factors and the number of falls recorded during follow-up was analysed by means of negative binomial regression with an overdispersion parameter estimated on the actual distribution of the dependent variable (i.e. number of falls). All frailty and cardiovascular factors were initially entered in a univariate negative binomial regression model, and those factors reaching statistical significance (p-value $\leq$ .05) were taken forward to the multivariate stage. The multivariate analysis consisted of a first model (Model 1), in which all factors were adjusted for clinical confounders, while a second model was designed to assess the second research hypothesis. In this second model (Model 2), frailty and physical function factors were adjusted for all variables in Model 1 and for the cardiovascular function variable showing the highest correlation (R^2) with number of falls, while cardiovascular factors were adjusted for all variables in Model 1 and for frailty. In a further analysis, we explored the goodness of fit of the regression models by reporting the relative change in Akaike's Information criterion (AIC) occurring when frailty and cardiovascular function were modelled together.

Sensitivity analyses were undertaken using the receiver operating characteristic (ROC) analysis of those potential factors associated with falls (yes or no), and the area under the curve (AUC) was used to compare the predictive ability of frailty alone with a model composed of frailty and a cardiovascular predictor. Statistical limits for significance were set at an alpha level of $p \leq .05$.

6.3 Results

6.3.1 Participants

The screening and recruitment details of the study were described in Chapter 3 (paragraph 3.3.1). Nine out of the 76 patients who were enrolled in the study (11.8%) were lost to follow-up due to renal transplantation (n= 4; 5.3%) and death (n= 5; 6.6%). However, 2 of these patients were retained in the data analysis because they had experienced falls during the prospective observational follow-up prior to renal transplantation/death. Therefore, 69 patients were entered in the final analysis.

6.3.2 Demographic and clinical characteristics

The demographic and clinical characteristics of the study participants are summarised in Table 3.1. Fallers were more likely to be prescribed antidepressants, and had significantly higher CRP compared to non-fallers. No statistically significant differences in other clinical characteristics were detected.

6.3.3 Falls

As previously reported in Chapter 3, paragraph 3.3.3, 26 of 69 patients (37.7%) experienced at least one fall during the 12-month observational follow-up. A total number of 80 falls were recorded, resulting in an incidence of 1.16 falls/patient-year. Figure 3.2 shows the distribution of number of falls occurred during the study period.

6.3.4 Frailty and physical function

The frailty and physical function characteristics of the study participants are summarised in Table 6.1. Fallers were more likely to meet the frailty component of self-reported exhaustion. In addition, fallers had significantly higher postural sway measures, such as AbsVel, VelX, VeY, and Area95, indicating a worse postural balance compared to non-fallers.

Table 6.1. Frailty and physical function characteristics of study participants: results are expressed as percentages for categorical variables and mean ± SD for continuous data.

Variables	All patients (69)	Fallers (26)	Non-fallers (43)	P-value
Frailty components and phenotype				
Low PA (n) (%)	33 (47.8)	12 (46.2)	21 (48.8)	0.829
Low gait speed (n) (%)	20 (29)	11 (42.3)	9 (20.9)	0.058
Low strength (n) (%)	33 (47.8)	12 (46.2)	21 (48.8)	0.829
Exhaustion (n) (%)	51 (73.5)	24 (92.3)	27 (61.9)	0.006
Unintentional weight loss (n) (%)	12 (17.6)	7 (28)	5 (11.6)	0.108
Fried's frailty phenotype (n) (%)	26 (37.7)	13 (50)	13 (30.2)	0.101
Objectively measured PA				

Time spent standing (h) (SD)	2.4 (1.2)	2.1 (1.1)	2.5 (1.2)	0.177
Time spent stepping (h) (SD)	0.7 (0.4)	0.6 (0.3)	0.8 (0.4)	0.218
Daily steps (n°) (SD)	3086 (1810)	2601 (1325)	3366 (2004)	0.144
Daily sit to stands (n°) (SD)	37.5 (12.6)	38.3 (16.1)	37.1 (10.3)	0.894
Strength				
Handgrip (Kg) (SD)	26.9 (9.5)	24.5 (10)	28.4 (9)	0.101
Leg extension (Kg) (SD)	20.1 (9)	17.4 (8.3)	21.8 (9.1)	0.050
Functional tests				
Gait speed (m/s) (SD)	0.85 (0.26)	0.78 (0.26)	0.9 (0.25)	0.067
TUG (s) (SD)	11.5 (4.8)	13.3 (6.4)	10.4 (3.4)	0.055
CSTS-5 (s) (SD)	17.1 (8.9)	19.6 (12.3)	15.7 (6.3)	0.355
Postural balance in EO				
RangeX (mm) (SD)	23.9 (11.4)	27.3 (13.4)	22 (9.6)	0.052
RangeY (mm) (SD)	28.5 (12.7)	31.5 (14.2)	26.8 (11.6)	0.078
RMSX (mm) (SD)	4.8 (2.5)	5.6 (3.2)	4.4 (2)	0.056
RMSY (mm) (SD)	5.6 (2.7)	6.3 (3.2)	5.2 (2.2)	0.132
AbsVel (mm/s) (SD)	40.9 (8.6)	43.6 (8.6)	39.3 (8.3)	0.013
VelX (mm/s) (SD)	26 (5.8)	27.6 (5.7)	25.1 (5.7)	0.017
VelY (mm/s) (SD)	26 (5.5)	28 (5.8)	24.9 (5.1)	0.010
Area95 (mm^2) (SD)	2427 (3067)	3206 (4274)	1974 (1999)	0.039

Abbreviations: SD: standard deviation; PA: physical activity; TUG: timed up and go test; CSTS-5: 5 repetitions chair sit to stand test; EO: eyes open; RangeX: range of centre of pressure (COP) displacement along the medial-lateral (ML) axis; RangeY: range of COP displacement along the anterior-posterior (AP) axis; RMSX: root mean square displacement along the ML axis; RMSY: root mean square displacement along the AP axis; AbsVel: absolute velocity; VelX: velocity along the ML axis; VelY: velocity along the AP axis; Area95: 95% confidence ellipse area.

6.3.5 Cardiovascular function

The cardiovascular function characteristics of study participants at rest are summarised in Table 6.2, while the haemodynamic responses to HUT-60° are reported in Table 6.3.

Table 6.2. Cardiovascular function characteristics of study participants. Baroreflex and haemodynamic variables at rest: results are expressed as mean ± SD.

Variables	All patients (69)	Fallers (26)	Non-fallers (43)	P-value
Baroreflex function				
Up-ramps (n°) (SD)	20.4 (18.9)	20.9 (22.9)	20.1 (15.8)	0.632
Down-ramps (n°) (SD)	18.4 (15.9)	19.1 (18.3)	17.9 (14.2)	0.811
Total-ramps (n°) (SD)	38.8 (34.3)	40 (40.7)	38 (29.8)	0.688
Up-events (n°) (SD)	4.5 (7.1)	2.6 (3.7)	5.7 (8.4)	0.125
Down-events (n°) (SD)	4.8 (6.4)	3.3 (4.5)	5.7 (7.3)	0.347
Total-events (n°) (SD)	9.3 (13)	6 (7.9)	11.4 (15.1)	0.129
Up-BEI (%) (SD)	20.6 (25.2)	14.6 (20.2)	24.7 (27.7)	0.165
Down-BEI (%) (SD)	27.9 (26.4)	20.3 (22.7)	32.9 (27.7)	0.103
Total-BEI (%) (SD)	25.4 (25)	17.7 (19.1)	30.6 (27.4)	0.078
BRS (ms/mmHg) (SD)	9.3 (7.1)	10.3 (9.3)	8.8 (5.9)	0.806
Haemodynamic variables				
RRI (ms) (SD)	894.9 (163.1)	867.7(112.4)	911.4 (186.8)	0.240
HR (bpm) (SD)	69.5 (12)	70.7 (9.3)	68.8 (13.4)	0.506
contSBP (mmHg) (SD)	124 (23.1)	127 (26.2)	122.1 (21.1)	0.462
contDBP (mmHg) (SD)	77.8 (14.8)	76.8 (12.5)	78.4 (16.1)	0.756
contmBP (mmHg) (SD)	97.2 (17.7)	97.9 (16.9)	96.8 (18.4)	0.801
SV (ml) (SD)	64.4 (14.4)	63.6 (12.1)	64.8 (15.7)	0.921
CO (L/min) (SD)	4.4 (1.2)	4.5 (0.9)	4.4 (1.3)	0.416
TPR (dyne*s/cm^5) (SD)	1777 (501)	1716 (371)	1816 (570)	0.440
SI (ml/m^2) (SD)	34.8 (8.8)	35.2 (7.8)	34.5 (9.5)	0.455
CI (L/min*m^2) (SD)	2.4 (0.7)	2.5 (0.5)	2.4 (0.8)	0.167
TPRI(dyne*s*m^2/cm^5) (SD)	3330 (1037)	3121 (710)	3464 (1190)	0.154
TFC (1/kOhm) (SD)	32.9 (10.8)	34.6 (12.1)	31.9 (10)	0.365
OscSBP (mmHg) (SD)	128.2 (22)	134.4 (26.3)	124.8 (18.7)	0.094
OscDBP (mmHg) (SD)	81 (13.9)	82.4 (12.8)	80.2 (14.5)	0.553

Abbreviations: SD: standard deviation; Up-BEI: up-events baroreceptor effectiveness index; Down-BEI: down-events baroreceptor effectiveness index; Total-BEI: total-events baroreceptor effectiveness index; BRS: baroreflex sensitivity; RRI: R-R interval; HR: heart rate; contSBP: continuous systolic blood pressure; contDBP: continuous diastolic blood pressure; contmBP: continuous mean blood pressure; SV: stroke volume; CO:

cardiac output; TPR: total peripheral resistance; SI: stroke index; CI: cardiax index; TPRI: total peripheral resistance index; TFC: thoracic fluid content; OscSBP: oscillometric systolic blood pressure; OscDBP: oscillometric diastolic blood pressure.

No differences in baroreflex/haemodynamic function, as assessed at rest or in response to HUT-60°, were detected between fallers and non-fallers.

Table 6.3. Haemodynamic responses to HUT-60°: results are expressed as mean ± SD.

Variables	All patients (69)	Fallers (26)	Non-fallers (43)	P-value
RRI (ms) (SD)	-60.4 (66.8)	-55.9 (71.1)	-63 (65)	0.514
HR (bpm) (SD)	6.2 (7.3)	6.9 (9.6)	5.8 (5.7)	0.860
contSBP (mmHg) (SD)	3.9 (11.9)	4.8 (14.9)	3.4 (9.9)	0.178
contDBP (mmHg) (SD)	6.3 (8.5)	6.3 (10.6)	6.3 (7.1)	0.575
contmBP (mmHg) (SD)	5.3 (9.4)	5.4 (12)	5.2 (7.8)	0.436
SV (ml) (SD)	-4.1 (13.8)	-4.5 (12.7)	-3.9 (14.5)	0.693
CO (L/min) (SD)	0.01 (1)	0 (0.9)	0.02 (1)	0.734
TPR (dyne*s/cm^5) (SD)	98.3 (374.8)	102.8(367.4)	95.5 (384.1)	0.941
SI (ml/m^2) (SD)	-2.3 (7.6)	-2.3 (6.9)	-2.3 (8)	0.703
CI (L/min*m^2) (SD)	-0.01 (0.5)	0.01 (0.5)	-0.01 (0.5)	0.887
TPRI(dyne*s*m^2/cm^5) (SD)	173.7 (684)	193.8 (655.3)	161.3 (709)	0.856
TFC (1/kOhm) (SD)	-1.9 (1.8)	-2 (1.9)	-1.8 (1.8)	0.632
OscSBP (mmHg) (SD)	-3.6 (9.8)	-5.6 (10.9)	-2.5 (9)	0.249
OscDBP (mmHg) (SD)	-0.7 (6.9)	-2.6 (7.5)	0.3 (6.4)	0.432

Abbreviations: SD: standard deviation; RRI: R-R interval; HR: heart rate; contSBP: continuous systolic blood pressure; contDBP: continuous diastolic blood pressure; contmBP: continuous mean blood pressure; SV: stroke volume; CO: cardiac output; TPR: total peripheral resistance; SI: stroke index; CI: cardiax index; TPRI: total peripheral resistance index; TFC: thoracic fluid content; OscSBP: oscillometric systolic blood pressure; OscDBP: oscillometric diastolic blood pressure.

6.3.6 Predictors of falls

In univariate negative binomial regression analysis, frailty and physical function measures such as number of daily steps, number of daily sit to stands, handgrip, gait speed, and TUG predicted a higher number of falls. In addition, total-BEI and the responses of CO and OscDBP to HUT-60° also predicted a higher number of falls (Table 6.4).

All frailty/physical function and cardiovascular function factors reaching statistical significance in univariate analysis were adjusted in Model 1 for CRP and antidepressant use, as we identified these variables as potential clinical confounders (Table 3.1). Moreover, with concern for multi-collinearity, we only reported the baroreflex function index showing the highest correlation with number of falls (total-BEI). In fully adjusted analyses (Model 2), total-BEI, and the haemodynamic response of OscDBP to HUT-60° were associated with a higher number of falls.

Table 6.4. Negative binomial regression analysis: predictors of falls.

	Univariate		**Multivariate**			
			Model 1		**Model 2**	
Factors	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
Frailty & physical function						
Frailty (yes/no)	4.10 (1.60-10.51)	0.003	2.23 (0.85-5.87)	0.103	1.78 (0.70-4.51)	0.224
Daily steps (n°)	0.99 (0.99-1.00)	0.006	1.00 (0.99-1.00)	0.137	1.00 (0.99-1.00)	0.106
Daily sit to stands (n°)	0.96 (0.93-0.99)	0.042	0.98 (0.94-1.02)	0.387	0.99 (0.95-1.04)	0.707
Handgrip (Kg)	0.94 (0.88-0.99)	0.034	0.97 (0.92-1.02)	0.216	0.98 (0.93-1.04)	0.448
Gait speed (m/s)	0.08 (0.01-0.62)	0.016	0.26 (0.03-2.08)	0.205	0.36 (0.04-3.32)	0.363
TUG (s)	1.16 (1.02-1.32)	0.021	1.08 (0.96-1.21)	0.220	1.03 (0.91-1.17)	0.643
Cardiovascular function						
Total-BEI (%)	0.96 (0.93-0.98)	<0.001	0.96 (0.94-0.99)	0.003	0.96 (0.94-0.99)	0.004
CO (L/min)	0.51 (0.27-0.98)	0.043	0.66 (0.37-1.15)	0.143	0.67 (0.39-1.13)	0.134
OscDBP (mmHg)	0.90 (0.83-0.98)	0.010	0.93 (0.87-0.99)	0.036	0.93 (0.87-0.99)	0.033

Abbreviations: RR: rate ratio; CI: confidence interval; TUG: timed up and go test; Total-BEI: total-events baroreceptor effectiveness index; CO: cardiac output response to HUT-60°; OscDBP: oscillometric diastolic blood pressure response to HUT-60°; Model 1: All factors are adjusted for CRP and antidepressant use; Model 2: Frailty and physical

function factors are adjusted for all variables in Model 1 and for Total-BEI. Cardiovascular function factors are adjusted for all variables in Model 1 and for frailty.

Table 6.5 shows the goodness of fit (AIC) of the univariate regression models and its relative change following forced entry modelling of frailty and cardiovascular function (multivariate stage). The multivariate model composed of frailty and total-BEI resulted in a 19.1% decrease in AIC compared to frailty alone.

Table 6.5. Further analyses: goodness of fit of regression models.

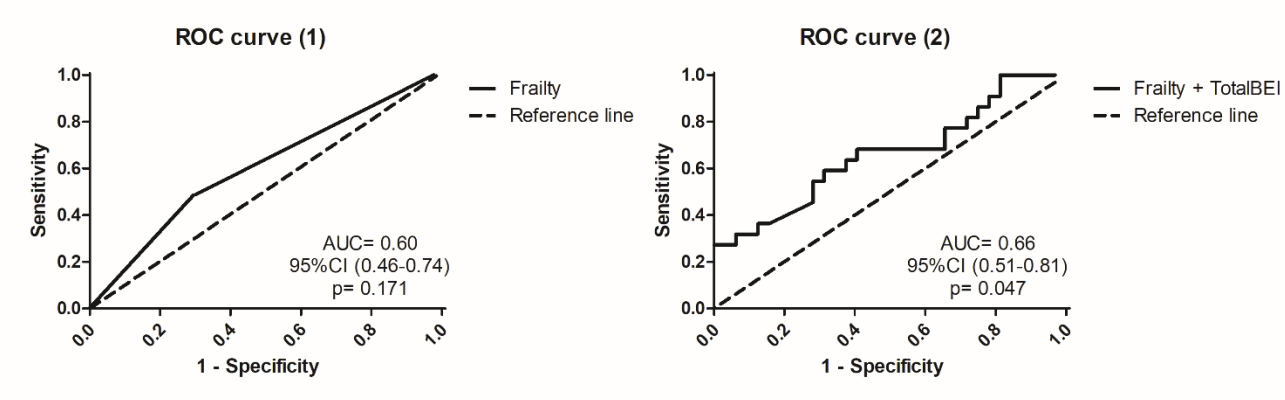
	Univariate			**Multivariate***			
Factors	**RR (95% CI)**	**P-value**	**AIC**	**RR (95% CI)**	**P-value**	**AIC**	**ΔAIC**
Frailty and physical function							
Frailty (yes/no)	4.10 (1.60-10.5)	0.003	185	2.53 (0.96-6.70)	0.060	149.6	***-19.1%***
Daily steps (n°)	0.99 (0.99-1.00)	0.006	142.3	1.00 (0.99-1.00)	0.036	113.2	***-20.4%***
Daily sit to stands (n°)	0.96 (0.93-0.99)	0.042	146.7	0.99 (0.95-1.03)	0.543	116.7	***-20.4%***
Handgrip (Kg)	0.94 (0.88-0.99)	0.034	188.6	0.97 (0.91-1.03)	0.330	151.8	***-19.5%***
Gait speed (m/s)	0.08 (0.01-0.62)	0.016	176.3	0.14 (0.02-1.39)	0.094	141.1	***-20.0%***
TUG (s)	1.16 (1.02-1.32)	0.021	171.7	1.10 (0.95-1.27)	0.226	138.5	***-19.3%***
Cardiovascular function							
Total-BEI (%)	0.96 (0.93-0.98)	<0.001	150.8	0.96 (0.94-0.99)	0.003	149.6	***-0.8%***
CO (L/min)	0.51 (0.27-0.98)	0.043	168.6	0.58 (0.33-1.04)	0.068	165.7	***-1.7%***
OscDBP (mmHg)	0.90 (0.83-0.98)	0.010	144.1	0.92 (0.85-0.99)	0.028	142.6	***-1.0%***

Abbreviations: RR: rate ratio; CI: confidence interval; AIC: Akaike's information criterion; TUG: timed up and go test; Total-BEI: total-events baroreceptor effectiveness index; CO: cardiac output; OscDBP: oscillometric diastolic blood pressure; *Frailty and physical function variables are adjusted by Total-BEI, cardiovascular function variables are adjusted by frailty.

6.3.7 Sensitivity analyses

Figure 6.1 shows the ROC curves of frailty alone and the model composed of frailty and total-BEI. Frailty alone did not discriminate significantly fallers from non-fallers, while adding the cardiovascular variable total-BEI resulted in a significant improvement of the AUC. Postural balance was the only factor that individually discriminated significantly fallers from non-fallers, and VelY (Appendix XVIII), in particular, showed the best predictive ability (AUC= 0.69, 95%CI: 0.55-0.82, p= 0.01).

Figure 6.1. Sensitivity analyses: ROC curve analysis.



Abbreviations: AUC: area under the curve; CI: confidence interval.

6.4 Discussion

We hypothesised that frailty and cardiovascular function would be associated with a higher number of falls in CKD-5 patients on HD. Additionally, we hypothesised that modelling the risk of falling by adding a cardiovascular function variable to frailty would improve the prediction of falls sustained over 12 months in this patient population.

The univariate negative binomial regression analysis revealed that frailty and other physical function measures, such as number of daily steps and sit to stands, handgrip strength, gait speed, and TUG were associated with a higher number of falls in the study population. In addition, cardiovascular function indices such as total-BEI, CO and OscDBP responses to HUT-60° were also associated with a higher number of falls (Table

6.4). However, in multivariate analysis, only total-BEI and the OscDBP response to HUT-60° were significantly predictive of a greater number of falls. In addition, modelling the risk of falling by adding a cardiovascular function index (total-BEI) to frailty resulted in a 19.1% reduction in AIC, indicating a better goodness of fit, while adding frailty to cardiovascular indices such as total-BEI, CO and OscDBP responses to HUT-60°, hardly modified the AICs (-0.8% to -1.7%, Table 6.5). Moreover, the sensitivity analyses performed by means of ROC curve analysis revealed that adding total-BEI to the frailty model corresponded to a net 6% improvement of the AUC and resulted in a statistically significant prediction of falling status (Figure 6.1).

The overall implications of these findings are that the addition of a baroreflex function index to an exclusively physical frailty-based model, did not only improve the prediction of falls, but it also highlighted the greater relative importance of a cardiovascular function index, implicated in the short-term regulation of BP, in predicting the occurrence of these falls. In particular, the forced entry modelling performed in Model 2 of the negative binomial regression analysis (Table 6.4) suggests that lower baroreflex function and orthostatic decrements of BP may have a higher impact than frailty on the prediction of falls in CKD-5 patients on HD.

The predominant role of these cardiovascular factors appeared to be also indirectly confirmed by the falls-related symptomatology reported by study participants (Chapter 3, Figure 3.3). The most common precipitating factors reported by fallers were dizziness/loss of consciousness (41.3% of falls), followed by loss of balance/unsteadiness of the legs (31.3% of falls), and environmental hazards (20% of falls). These symptoms seem to point out that the majority of falls were probably related to some underlying cardiovascular/haemodynamic type of mechanism. Because impairments of baroreflex function are linked to orthostatic decrements of BP (Mattace-Raso et al., 2007), the dysregulation of BP during a sudden change in body position, or during prolonged standing may be one of the main mechanisms implicated in the aetiology of falls in CKD-5 patients on HD. Both of these factors predicted a higher number of falls in our study.

Many dialysis-specific or idiopathic risk factors may be involved in the dysregulation of BP which could possibly lead to dizziness symptoms and falls in this clinical population.

First of all, the uremia-related cardiac autonomic dysfunction, characterised by alterations of the sympathetic, parasympathetic, and baroreflex components of the autonomic nervous system, is a factor that has been linked to symptomatic hypotension in CKD-5 patients (Robinson et al., 2002). Moreover, autonomic neuropathy, a common clinical complication of advanced diabetes and the most common cause of CKD (GBD, 2015), can also lead to a diminished response of BP to standing (Vinik et al., 2018). Secondly, dialysis patients are often treated with one or more antihypertensive drugs (83.8% and 51.5% of patients in our study). While this is often an unavoidable therapy for the treatment of hypertension, such antihypertensive polypharmacy has been linked to an increased risk of falling by inducing dizziness and postural hypotension (Tinetti et al., 2014). Thirdly, some research has postulated that fluid shifts, as part of regular HD, may pose these patients at risk of postural dizziness in the immediate post-dialysis period (Roberts et al., 2003). Our findings on the timing of falls recorded throughout the study do not support this last hypothesis, as only 8.3% of falls occurred after HD (Chapter 3, paragraph 3.3.4.4).

As expected from the findings of Chapter 5 (Table 5.3), diabetic nephropathy as PRD was significantly associated with a higher number of falls in univariate negative binomial regression analysis (RR: 3.0, 95%CI: 1.042-8.639, p= 0.042), which indirectly highlights how diabetes may be a confounding factor on the findings relating to the relationship between baroreflex function/haemodynamic responses to HUT-60° and falls. However, on a separate multivariate negative binomial regression analysis adjusted for diabetic status, baroreflex function assessed by means of total-BEI (RR: 0.961, 95%CI: 0.936-0.986, p= 0.003), and the CO response to HUT-60° (RR: 0.548, 95%CI: 0.306-0.982, p= 0.043) were still predictive of a higher number of falls. Interestingly, the OscDBP response to HUT-60° was no longer significantly associated with falls when the analysis was adjusted for diabetic status (RR: 0.945, 95%CI: 0.859-1.039, p= 0.240), which may reflect once again the mediating effect of diabetes on the study findings.

The estimates of association between frailty and number of falls experienced emerging from this study are remarkably similar to those observed by McAdams-DeMarco et al., (2013), who also explored the association between the Fried's frailty phenotype and falls.

In their study, authors found that frailty roughly predicted a three-fold higher number of falls in univariate Poisson regression analysis, while we found an approximately four-times higher number of falls predicted in the univariate regression (Table 6.4). The slightly higher estimate observed in our study may be due to the fact that we recorded falls for a longer observational period (12 months vs 6 months), and therefore frail patients in our study may have experienced a significantly higher number of falls, as also evidenced by the higher incidence of falls recorded in our study (1.16 vs 0.74 fall/person-year), which is likely to have resulted in a slightly more inflated rate ratio (4.1 vs 3.55). It should also be noted that a meaningful comparison of the predictive estimates emerging from the two studies is possible considering the univariate model only, as we adjusted the model for another predictor of falls (total-BEI) in order to address the second research hypothesis, whereas McAdams-DeMarco et al., (2013) adjusted the model for a number of classic demographic and clinical characteristics. Therefore, the two multivariate models represent different clinical findings and their interpretation should be applied with caution.

It should also be acknowledged that, although the negative binomial regression analysis revealed that postural balance did not predict a higher number of falls in the study participants, fallers had significantly higher postural sway measures, meaning a worse postural balance (Maki et al., 1994), compared to non-fallers (Table 6.1). Moreover, the ROC analysis showed that, among all physical function variables, postural balance was the only factor to significantly discriminate fallers from non-fallers, with VelY showing the highest AUC (Appendix XVIII). This finding indicates that, despite the apparent lack of association with number of falls, postural balance may still have a significant prognostic value of falling status in CKD-5 patients on HD.

Interestingly, the exploratory independent comparisons of fallers and non-fallers revealed that those who fell were more likely to use antidepressants (50% vs 23.8%) and had higher CRP levels (37.6±59.2 mg/L vs 18.3±32.7mg/L). Because both antidepressant use and high CRP have been linked to a higher risk of falling by previous research conducted on HD patients (Desmet et al., 2005; Kono et al., 2018), we adjusted the analysis for these possible clinical confounders (Model 1). In this first model of multivariate analysis, neither frailty nor the additional physical function measures were significantly associated

with a higher number of falls (Table 6.4). This finding further reinforces the observation that total-BEI and the OscDBP response to HUT-60° had a greater relative importance than frailty in predicting the number of falls experienced by study participants during the 12-month follow up.

6.4.1 Study limitations

It should be acknowledged that because the sample size was relatively small we could not apply a more exhaustive, a priori, multivariate negative binomial regression analysis to more robustly test the interrelationships between frailty/physical function, cardiovascular function, and falls. In addition, we should also acknowledge that, while orthostatic decrements of OscDBP were significantly associated with falls (Table 6.4), orthostatic decrements of OscSBP were not. However, in univariate negative binomial regression analysis, OscSBP decrements also exhibited a potential trend of association with falls (RR: 0.95, 95%CI: 0.89-1.01, p= 0.084), and it is possible that a larger sample size may have also resulted into better chances of detecting a significant association between OscSBP decrements and falls, by decreasing the chances of committing a type II error.

6.4.2 Conclusions

In conclusion, this prospective cohort study indicates that by adding a cardiovascular index, implicated in the short-term regulation of BP, to a frailty-only model it was possible to improve significantly the prediction of falls in CKD-5 patients on HD. Baroreflex function, as assessed by means of BEI, and orthostatic decrements of BP showed a higher impact, and thus greater relative importance, than frailty in predicting number of falls in this clinical population. Therefore, findings from this study challenge the current assumption that frailty is primarily involved in the aetiology of falling in people living with CKD-5. The clinical implications of these findings indicate that a simple non-invasive, time-efficient, assessment consisting of a continuous and simultaneous recording of BP and HR may be more useful than frailty assessment alone when predicting falls in HD patients. A high number of falls appear to be mediated by a degree of cardiovascular dysregulation, evidenced by the predominance of self-reported dizziness

symptoms. We therefore recommend that interventions designed to improve baroreflex function/short-term regulation of BP should be included when implementing falls prevention programmes in this patient population.

In addition, an assessment of postural balance by means of a force platform also showed to have a significant predictive value in ROC curve analysis. Postural balance is usually not incorporated in frailty assessments, and it may be a further meaningful outcome to evaluate in the context of falls prediction and prevention in HD patients.

CHAPTER 7: GENERAL DISCUSSION AND CONCLUSIONS

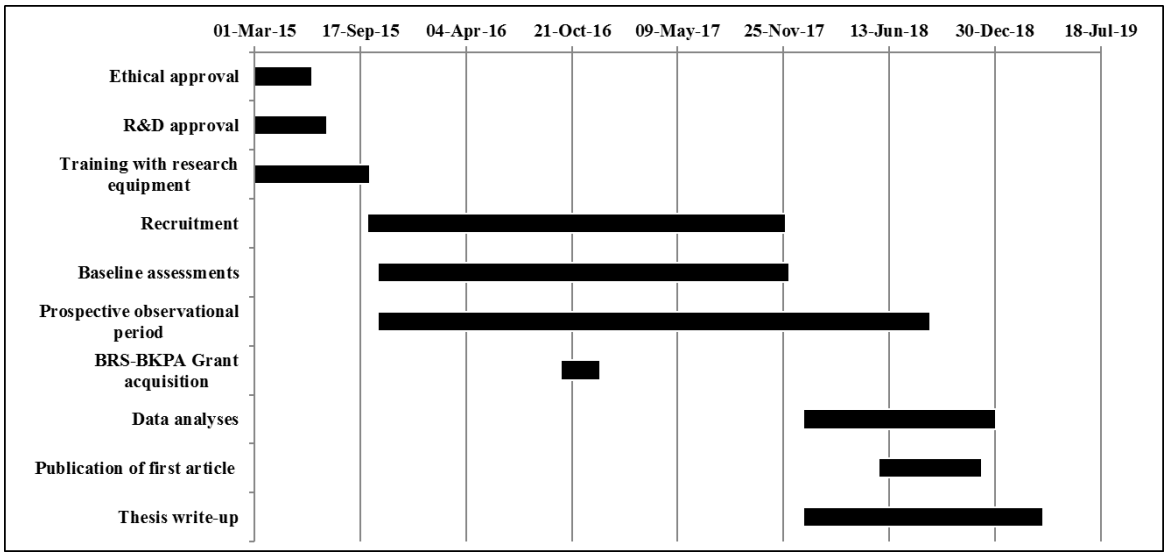
7.1 Research project management

The timeline and milestones of this PhD research project are summarised in Figure 7.1. From the moment of first submission to the REC (31/03/2015), the ethics of the study were reviewed and approved in 80 days, which is generally considered a relatively rapid time to gain ethical approval for research based in a healthcare environment (Smith-Merry et al., 2014; Varley et al., 2016). Patient recruitment was a crucial aspect of the research project, as evidenced by the lengthy process (roughly 25 months) shown in Figure 7.1. Although the recruitment rate achieved (35.3%) was reasonable, considering that CKD-5 patients on HD are a group of people with multiple barriers to clinical research participation (Flythe et al., 2017), the time necessary to enrol an adequate sample size resulted in a delay of the observational follow-up period completion (August 2018). In the context of this PhD study, the main barrier to research participation that emerged from the recruitment process was unwillingness of patients to travel to the hospital on an extra day to complete the baseline assessments. While this is an understandable reason of why many patients declined to take part in our research, given that HD is an extremely time-demanding treatment and patients often feel overwhelmed with the amount of time spent at the hospital (Kopple et al., 2017), the study design dictated that participants had to complete all baseline assessments on a non-HD day to optimise the standardisation of testing procedures (Chapter 2, paragraph 2.5.1.3). It is possible that performing data collection on a HD day could have inflated the recruitment rate, with consequent higher number of participants in the study. However, the stricter testing conditions used in our study are likely to have impacted positively on the quality of all data collected, for the reasons described in paragraph 2.5.1.3, as well as on external validity and generalisability of study findings.

According to the original REC submission, patients were initially recruited only from the North Lanarkshire (Monklands Hospital) research site until December 2016. However, after the acquisition of a British Renal Society – British Kidney Patient Association (BRS-

BKPA) grant (16-003), awarded in December 2016, we were able to continue patient recruitment until November 2017 in a second research site in Fife (Victoria Hospital).
The research data were preliminarily explored starting from January 2018 to allow the preparation of two abstracts that were presented at the European Renal Association – European Dialysis & Transplant Association (ERA-EDTA) Congress 2018 and at the UK Kidney week (UKKW) 2018. A first research article (Appendix XIX) was published in December 2018 and data analysis was also completed in December 2018. The first draft of the PhD thesis was produced by February 2019, and its revised version was submitted in June 2019.

Figure 7.1. GANTT chart of study timeline and milestones.



7.2 Research findings

7.2.1 Estimates of falls' risk in CKD-5 patients on HD

One of the most important premises upon which the rationale of this PhD research project was developed is that the population of CKD-5 patients on HD is at high risk of falls, as evidenced by previous studies (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; Farragher et al., 2014; Polinder-Bos et al., 2014; Kono et al., 2018) that were described in Chapter 1.

The findings on the estimates of falls from this PhD programme of research were reported and discussed in Chapter 3. It should be acknowledged that, because a healthy and age-matched control group was not assessed, we can only interpret these findings by critically comparing them with the current body of literature reporting information on the risk of falls in the non-uraemic population. Both the prevalence of study participants experiencing at least one fall during the 12 month follow-up (37.7%), and the incidence of falls/person-year (1.16) emerging from this PhD are aligned with the findings from previous studies (Desmet et al., 2005; Roberts et al., 2007), and most importantly they reinforce the evidence that HD patients are a clinical population at high risk of falls (Lopez-Soto et al., 2015).

One of the most valuable methodological improvements in this PhD research programme compared to previous studies was that falls related data were prospectively and contemporaneously recorded by a researcher, as close to the falling event as possible. Therefore, the resulting estimates of falls are less likely to be subjected to significant recall biases and misreporting (Hauer et al., 2006). To the best of our knowledge, this is the seventh out of eight prospective studies (conducted in HD patients) reporting an incidence of falls/person-year higher than in community-dwelling older adults (≥ 65 years), an established group of people at high risk of falls (WHO 2008).

Because the mean age of fallers in our study was approximately 58 years, we are led to think that HD patients are predisposed to a high risk of falling even before the onset of older age (65 years old), an observation also supported by previous research that reported a similar risk of falls in young and older HD patients (McAdams-DeMarco et al., 2013). The WHO global report on falls prevention in older age states that about 30% of community-dwelling older (>65 years) adults fall at least once every year (WHO, 2008). This estimate may seem to suggest that our study population could have a similar falls' risk profile to the general elderly population (37.7% of patients falling at least once in 12 months). Despite the observation that CKD patients experience this risk at younger age, an additional distinction in terms of the aetiology of falling should be made. A further merit of our study design is that, as part of the observational follow-up, we documented the precipitating factors occurring immediately prior to any fall. These additional data

revealed that most falls (41.3%) were associated with the occurrence of dizziness symptoms, followed by loss of balance/strength (31.3%), and only 20% of falls were precipitated by environmental factors such as a slip or trip. Because previous research has reported that the large majority of falls (77%) in healthy older adults are due to slipping/tripping accidents resulting from environmental hazards (Hill et al., 1999), it is plausible that many of these falls could be prevented. In particular, falls risk might be reduced if the potential fallers increased their attention to environmental hazards and/or through the improvement of the local environment (e.g. wet surfaces, poor lighting, obstacles etc.). Conversely, HD patients may suffer a greater number of falls due to more structured physiological impairments of cardiovascular and physical function (Roberts et al., 2003; McAdams-DeMarco et al., 2013), making these falls more difficult to prevent without recourse to structured physical rehabilitation. In addition, many falls prevention policies are already operationalised in dialysis facilities by the nursing staff (Kliger et al., 2006; Heung et al., 2010), who typically seek to promote safety by minimising environmental risk factors (Garrick et al., 2015). Moreover, many HD patients have access to occupational therapy services which also focus on the reduction of environmental hazards in daily life to prevent falls (Woodland et al., 2003). These observations seem to suggest that, in comparison to community-dwelling older adults, the population of CKD-5 patients on HD may benefit already from a general safety culture promoted by nursing and occupational therapy staff. However, the estimates of falls reported in dialysis populations are still considerably higher than those seen in the non-uraemic geriatric population (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; Farragher et al., 2014).

While many falls in healthy older adults seem to be of accidental aetiology and may be associated with increased engagement in physical activities such as jogging or fast walking (with and without sudden accelerations) that could lead to falls/slips/trips (Hill et al., 1999) it is noteworthy that HD patients tend to be extremely inactive (Johansen et al., 2010). The very low number of daily steps recorded for our study participants (Chapter 4, Table 4.2) reinforces this idea. Another factor that is reported to influence sedentary behaviour in this patient group is fear of falling (Jayaseelan et al., 2018). Consequently,

physical activity avoidance may paradoxically reduce the occurrence of falls in HD patients compared to healthy older adults. Unsurprisingly, this is not an effective strategy to prevent falls in the long term, as limiting physical activity is one of the elements involved in initiating the vicious circle of frailty (Fried et al., 2001), and it is linked to a cascade of negative health outcomes (Cecchini et al., 2010; Johansen et al., 2018).

7.2.2 Frailty, physical function, and falls in HD patients

One of the objectives of this PhD thesis was to explore the relationship between frailty, physical function, and falls in the population of CKD-5 patients on HD. Both frailty and physical function measures are linked to an increased risk of falling in community-dwelling older adults (Fried et al., 2001; Shumway-Cook et al., 2000; Ward et al., 2015). Because there is now strong evidence that the prevalence of frailty in the CKD-5 population is much higher than in community-dwelling elderly individuals (36.8% vs 7%), as reported by a recent systematic review with meta-analysis (Kojima et al., 2017), we hypothesised that this syndrome may have a great impact on falls in HD patients. Indeed, recent observational studies highlighted that frailty may be one of the predominant risk factors for falls and fall-related injuries in dialysis populations (McAdams-DeMarco et al., 2013; Kutner et al., 2014; Delgado et al., 2015).

Although frailty and physical function are intrinsically related (Fried et al., 2001), relatively few studies have examined the relationship between low physical function and falls, with contrasting findings as to which measures may better predict falls in HD patients (Chapter 1, paragraph 1.2.3.4). Moreover, due to time and resource constraints or other logistic issues, some of these studies exclusively reported data on self-reported measures of physical function and frailty (Polinder-Bos et al., 2014; Delgado et al., 2015), which are generally considered less reliable and accurate than objective assessments.

In Chapter 4 of this PhD thesis we sought to address these common methodological issues by performing a comprehensive assessment of objectively measured frailty and physical function, and by exploring the association of these factors with the falling status of study participants. We also aimed to identify which frailty/physical function components are

more strongly associated with falls in order to pinpoint possible rehabilitation strategies for falls prevention in HD patients.

7.2.2.1 Frailty and falls

An important preface to this discussion section is that, while there is a general agreement in defining frailty as a syndrome of decreased resistance to stressors describing a state of increased vulnerability to various health problems (Fried et al., 2001; McMillan et al., 2012), there are two main conceptualisations of this state. Fried et al., (2001) developed an approach to frailty, whose predominant feature is the physical function deterioration mainly arising from sarcopenia, while a second approach is portrayed by the Frailty Deficit Accumulation Index (Rockwood et al., 2007), an instrument that focuses on the accumulation of deficits across multiple systems. The reported prevalence of frailty in the population of CKD-5 patients on HD does not seem to differ substantially when measured by means of either of the two methods (Painter et al., 2013; Salter et al., 2015; Alfaadhel et al., 2015; Isayere et al., 2016; Drost et al., 2016; Kojima et al., 2017). However, it should be acknowledged that the relationship with falls (or other clinical outcomes) may vary significantly according to the operationalisation of frailty used. For instance, the prevalence of the Fried's frailty phenotype in our study was about 37%, an estimate approximately two times higher than the prevalence from another study conducted in dialysis patients that assessed frailty with the FRAIL scale (Chao et al., 2015). Thus, these methodological discrepancies may impact greatly on the estimated magnitude of association between frailty and falls.

At least three studies have presently investigated the relationship between frailty and falls, or falls-related fractures in HD patients, and they all concluded that frailty is a significant risk factor for falls in this clinical population (McAdams-DeMarco et al., 2013; Kutner et al., 2014; Delgado et al., 2015). Out of these studies, our investigation is more similar to the work by McAdams-DeMarco et al., (2013), from a methodological point of view, because both studies employed the Fried's frailty phenotype, a prospective design, and the same operational definition of a "fall". Not surprisingly, the results were similar as both

studies found that frailty was associated with a roughly 3-fold higher risk of falls (Chapter 4, Table 4.5).

Frailty, as assessed in our study, is closely related to sarcopenia (Fried et al., 2001), a typical geriatric syndrome whose diagnosis entails low muscle mass and impaired physical function (Cruz-Jentoft et al., 2010). The loss of muscle mass and function is inevitable with ageing due to the hormonal changes and declines across various physiologic systems (Frontera et al., 2017), however, in the context of CKD-5, these processes are accelerated by chronic inflammation and oxidative stress, as well as by other CKD-specific factors including acidemia, hyperphosphataemia, and hypernatremia (Kooman et al., 2014). Therefore, these pathophysiological abnormalities may also be indirectly implicated in the aetiology of falling in HD patients and, as we observed in our study, they may confound the well-established relationship between ageing and falling. The finding that fallers were younger than 65 years old, and generally even younger than non-fallers (although non-significantly) may reflect the premature ageing of HD patients (Kooman et al., 2017).

Physical inactivity and exhaustion seemed to be the main factors driving the significant association between frailty and falls observed in the current study, as the distribution of only these two frailty components was significantly different between fallers and non-fallers (Chapter 4, Table 4.1). This finding is interesting for a couple of reasons. First of all, CKD-5 patients tend to avoid many physical activities due to fear of falling (Jayaseelan et al., 2018) which may deceptively reduce the occurrence of falls in the first place. However, in the long-run, this strategy may have catastrophic implications not only for the maintenance of a general good state of health but also for falls. The logistic and negative binomial regression analyses performed in Chapters 4 and 6 revealed that low PA levels, assessed by means of number of daily steps, were associated with the falling status of study participants (Table 4.5) and were also predictive of a higher number of falls (Table 6.4). This could mean that physical inactivity may both be an outcome of a fall suffered from a patient but also a significant predictor of future falls. Moreover, physical inactivity is also likely to indirectly increase exhaustion levels (through general deconditioning) observed in dialysis patients (Roshanravan et al., 2012). Unsurprisingly,

this was the other element of frailty observed to be significantly different between fallers and non-fallers (Table 4.1). Secondly, and perhaps more importantly, the finding that physical inactivity seemed to drive the association between frailty and falls has important implications for preventive and rehabilitative interventions. PA is often the frailty component most responsive to exercise interventions and, despite the possible fear of falling and objective functional limitations, the findings from this study strongly support the notion that HD patients should be encouraged to increase their PA levels to preserve independence and reduce their risk of falls in the long-term.

7.2.2.2 Physical function and falls

Physical function is one of the main constituents of frailty (Morley et al., 2013). The results from the exploratory analyses of frail versus non-frail study participants performed in Chapter 4 clearly revealed marked decreases for physical function performance in measures such as gait speed, TUG, and CSTS-5 in frail patients (Figure 4.3). The Fried's frailty phenotype defines slowness, assessed by means of gait speed, as one of the core elements of frailty (Fried et al., 2001). In our study, we also assessed TUG and CSTS-5 as additional physical function measures potentially linked to falls. Previous research conducted on community-dwelling older adults has suggested that cut-off values of 14 and 16.7 seconds, in the TUG and CSTS-5 respectively, are indicative of an increased risk of falling (Shumway-Cook et al., 2000; Ward et al., 2015). Although fallers tended to have a worse performance in these outcomes compared to non-fallers (Table 4.3 & Table 6.1), the independent comparisons performed in our study did not reveal any statistically significant differences between these two groups. Because two previous studies conducted on dialysis populations also did not highlight any significant differences between fallers and non-fallers in terms of TUG performance (Cook et al., 2006; Farragher et al., 2014), we may plausibly conclude that these measures are not useful in predicting falls in HD patients. However, more detailed analysis of the findings from these studies revealed that the mean TUG performance in the study population (11.5±4.8s) was poor compared with normative data from healthy elderly people, being 29% lower than individuals aged 60-69 years and comparable to the TUG reference values of those aged 80 years and older

(Bohannon et al., 2006). Secondly, in the study conducted by Shumway-Cook et al., (2000), participants were defined as fallers if they had experienced at least two falls in the previous 6 months, and the mean age of fallers was 86.2 years old, significantly higher than in the group of non-fallers, whose mean age was 78.4 years (p= 0.002). Consequently, the resulting difference in TUG performance between fallers and non-fallers (22.2±9.3s vs 8.4±1.7s) was significantly higher than the difference observed in our study (fallers: 13.3±6.4s vs non-fallers: 10.4±3.4s), and in the study by Farragher et al., (2014) (fallers: 11.7±2.6s vs non-fallers: 10.2±2.0s), in which the same definition of fallers was used. Therefore, the 14 seconds cut-off value proposed by Shumway-Cook et al., (2000) should be interpreted carefully by considering that different classifications of "fall" and "faller" will inevitably result in different cut-off values or degrees of relationship between risk factor and outcome.

Analogously, Ward et al., (2015) concluded that CSTS-5 performance is associated with falling, and that a cut-off value of 16.7 seconds is predictive of falls. In this study though, the operational definition of a fall was "an injurious fall leading to fractures/sprains/dislocations/pulled or torn muscles/ligaments/tendons, or to seeking medical attention", and the association between CSTS-5 and the risk of sustaining an injurious fall over 4 years was analysed. Therefore, the lack of association between CSTS-5 and falls observed in our study, and apparent discrepancy with the findings of Ward et al., (2015) should be contextualised in light of the different methodological approaches and prognostic implications. Notably however, the 16.7 seconds cut-off value proposed by Ward et al., (2015) seems to fit well in the context of our data, as fallers had a mean CSTS-5 performance of 17.7±10s as opposed to non-fallers, whose mean performance was 16.2±7s (Table 4.3).

It should also be noted that, while no association between TUG/CSTS-5 and falls was found in logistic regression analysis, the univariate negative binomial regression analysis revealed that both gait speed and TUG were predictive of a higher number of falls (Table 6.4). Nevertheless, these variables were no longer significantly associated with falls when the analysis was adjusted for conventional clinical status indicators such as CRP and antidepressant use (gait speed= RR: 0.26, 95%CI: 0.03-2.08, p= 0.205; TUG= RR: 1.08,

95%CI: 0.96-1.21, p= 0.220). Because we observed this association in negative binomial regression analysis, we cannot exclude that gait speed and TUG test may be useful instruments to predict falls in the population of CKD-5 patients on HD. However, we plausibly hypothesise that perhaps a composite score of physical function obtained from multiple field tests may be more useful than single assessments in detecting an increased risk of falling. For instance, a couple of recent prospective studies conducted on HD patients have concluded that the SPPB test, a composite assessment of physical function including the CSTS-5 among other tests (Ortega-Perez de Villar et al., 2018), was predictive of falls in multivariate regression analyses (Wang et al., 2017; Kono et al., 2018).

7.2.2.3 Physical activity and falls

Although the role of PA on falls has already been discussed, in part, in the last paragraph of section 7.2.2.1, some observations emerging from the study need to be further examined. First of all, the PA status of the study population was assessed by means of subjective and objective measurements, both of which revealed a significant sedentary behaviour comparable to the findings on PA estimates in HD patients from the current literature. For instance, 47.2% of the study participants met the low PA component of frailty (Chapter 4, Table 4.1), an estimate that mirrors the findings from the large scale study DOPPS, which reported that 44% of dialysis patients never engage in any form of exercise (Tentori et al., 2010). Similarly, another investigation that assessed PA by means of the IPAQ questionnaire (the same instrument we used to categorise the low PA component of frailty) reported that 40% of HD patients were classified as completely inactive (Stringuetta-Belik et al., 2012). In addition, objective measurements of PA such as number of daily steps taken by the study participants (3129±1769, Table 4.2) were also consistent with the findings of Mafra et al., (2011), who reported that dialysis patients in their study walked an average of 2800 steps per day. Therefore, our findings on PA are indicative of marked sedentary behaviour (Tudor-Locke et al., 2004), and may be generalised to the population of CKD-5 patients on dialysis.

Although PA, as assessed by means of the ActivPal monitor, was not associated with increased odds of falling in multivariate logistic regression analysis (Table 4.5), patients classified as fallers had a significantly lower number of daily steps compared to non-fallers (Table 4.2). Additionally, objective measurements such as the number of daily steps and sit to stand transitions were associated with a higher number of falls in univariate negative binomial regression (Table 6.4). Moreover, low PA seemed to be one of the main drivers of the association observed between frailty and falls (Table 4.1). Therefore, although we cannot definitively conclude that physical inactivity is an independent risk factor for falls, our data suggest that low PA may be implicated in the aetiology of falling in HD patients.

To the best of our knowledge, only one other study examined the relationship between PA and falls in dialysis patients (Delgado et al., 2015). This investigation explored the association between a modified version of the Fried's frailty phenotype, consisting of three self-reported components (physical function, exhaustion, and PA), and falls or fractures in a large cohort of dialysis patients. The main findings of this study were that frailty was associated with time to first fall or fracture, and that the physical function (HR 1.33, 95% CI 1.01 – 1.75, p-value not reported) and exhaustion (HR 1.40, 95% CI 1.10 – 1.76, p-value not reported) components were also individually associated with an increased risk of falling. Physical inactivity had a similar point estimate (HR 1.36, 95% CI 0.78 – 2.37, p-value not reported) but it did not reach statistical significance in fully adjusted Cox regression analysis (Delgado et al., 2015). Even though the study could not provide evidence of a significant association with falls, one important observation should be highlighted to better interpret the meaning of these findings. In this study, the PA component of frailty was defined as a score in the lowest quintile of the Adjusted Activity Score of the Human Activity Profile (Johansen et al., 2001). This operationalisation of PA resulted in 94% of the study participants meeting the criteria of physical inactivity, a significantly higher estimate than what we found in our study (47.2%) and also contrasting with the prevalence of physical inactivity in dialysis populations emerging from the larger DMMS (35%) and DOPPS (44%) studies (O'Hare et al., 2003; Tentori et al., 2010). Therefore, as correctly acknowledged by the authors, the very small proportion of patients

classed as “physically active” may explain why the point estimate of PA did not reach statistical significance in their study (Delgado et al., 2015). Moreover, it is possible that a different operational definition of PA may have resulted in a significant association between this frailty component and falls also.

Although the findings from Delgado et al., (2015) and from our study do not provide ultimate evidence that physical inactivity contributes independently to an increased risk of falling in the population of CKD-5 patients on HD, they seem to suggest that increasing the levels of PA may be beneficial to the prevention of falls in this patient group. From a rehabilitation perspective, increasing the number of daily steps may be an effective preventive strategy to reduce the risk of falling, and it would also be a significantly low-cost intervention because it needs no or minimal supervision. A recent multicenter randomised clinical trial has shown that a simple walking program significantly improved physical function and quality of life in dialysis patients (Manfredini et al., 2017). However, future research is required to explore whether this kind of physical activity intervention is effective in reducing the occurrence of falls, among other adverse clinical outcomes, in HD patients.

7.2.2.4 Muscle strength and falls

One of the secondary objectives of this PhD thesis was to explore the relationship between muscle strength and falls in CKD-5 patients on HD. Low muscle strength is one of the defining components of the Fried’s frailty phenotype (Fried et al., 2001), an operationalisation of the frailty syndrome that has been consistently found to be associated with an increased risk of falling in HD patients (McAdams-DeMarco et al., 2013; Kutner et al., 2014). In addition, at least two systematic reviews, with meta-analysis, investigating the role of exercise on falls prevention have concluded that strength training should be incorporated in exercise-based interventions aimed to decrease falls in the community-dwelling population of older adults (Sherrington et al., 2011; Sherrington et al., 2017). Therefore, we hypothesised that muscle strength would be associated with falls in our study participants.

Although we expected to observe a strikingly lower muscle strength, as assessed by means of handgrip and leg extension, in fallers compared to non-fallers, this was not confirmed by our findings (Chapter 4, Table 4.3). Likewise, handgrip and leg extension strength were not associated with increased odds of falling in logistic regression analysis (Table 4.5). However, in Chapter 6, we found that low handgrip strength was associated with a higher number of falls in univariate negative binomial regression analysis (Table 6.4). Overall, the discrepancies emerging from Chapters 4 and 6 do not underpin any conclusive statements as to whether muscle strength is a useful predictor of falls in the CKD-5 population of HD patients. One important observation though is that, contrary to the current best practice recommendations on exercise prescription for falls prevention, which emphasise the greater utility of strength training compared to walking programs (Sherrington et al., 2011), low PA levels were more consistently associated with an increased risk of falling in our study population. Therefore, our findings seem to suggest that increasing PA may be more beneficial than strength training for the prevention of falls in this patient group.

However, because we only performed two assessments of muscle strength, we cannot exclude that this component of frailty may play an important role in the aetiology of falls in this clinical population, and perhaps other measurements of isometric/dynamic muscle strength could have revealed a stronger association with the risk of falling. For instance, Wang et al., (2017) recently reported that low ankle dorsiflexion strength was associated with a higher number of falls in a group of dialysis patients. Because a high number of falls are precipitated by tripping over an obstacle, or by a misstep (Timsina et al., 2017), both of which seem to be linked to poor ankle mobility/strength, we are led to think that this measure of strength may be more useful than isometric handgrip strength or isometric knee extension strength in predicting the risk of falling.

Another methodological limitation that should be acknowledged is that we did not perform any direct measurements of muscle mass in our study. The alteration of muscle quality/quantity would be an important factor mediating the relationship between strength and falls, as sarcopenia is also a known risk factor for falls (Zhang et al., 2019). Many CKD-related conditions such as elevated uraemia, increased glucocorticoid activity,

insulin resistance, metabolic acidosis, chronic inflammation, malnutrition, and the dialytic treatment itself can contribute to muscle wasting and loss of muscle strength in HD patients (Battaglia et al., 2016). Although we did not collect direct muscle mass characteristics, it should be noted that patients classified as fallers tended to have lower BMI (28±6.7kg*m^{-2} vs 30.3±5.6kg*m-2, p= 0.131), lower creatinine (617.4±173.7µmol/L vs 654.6±139.6µmol/L ,p=0.326), and higher CRP (28.7±49.8mg/L vs 17.6±33.4mg/L, p=0.083) than non-fallers. All of these characteristics seem to be associated with lower muscle mass and strength (Hamer et al., 2009; Wong et al., 2016; Kim et al., 2016). Although these differences were not statistically significant, they may be indicative of lower muscle mass in fallers, and therefore we cannot exclude that low muscle mass may also be a significant risk factor for falls in this clinical population.

7.2.2.5 Postural balance and falls

While the previous components of physical function assessed (PA, TUG, CSTS-5, muscle strength) were all implicitly linked to the Fried's frailty phenotype (Fried et al., 2001), postural balance is an element of physical performance independent from this construct of frailty. Although our results suggest that these factors are related, as frail participants consistently showed lower postural balance compared to those who were not frail (Chapter 4, Figure 4.4), an assessment of balance performance has never been incorporated in any operationalisation of frailty to the best of our knowledge. However, we decided to assess postural balance as a further potentially falls-related measure (King et al., 1995).

We found that fallers had worse postural balance than non-fallers in both Chapters 4 and 6 (Table 4.4 & Table 6.1). The logistic regression analysis also revealed that worse balance was significantly associated with increased odds of falling (Table 4.5). In addition, the ROC analysis performed in Chapter 6 showed that postural balance was the only factor to significantly discriminate fallers from non-fallers, with VelY showing the best predictive ability (AUC= 0.69, 95%CI: 0.55-0.82, p= 0.01). Nevertheless, balance performance was not associated with a higher number of falls in the negative binomial regression analysis performed in Chapter 6. To the best of our knowledge, this is the first study reporting a significant association between postural balance, as assessed by means of a force platform,

and falls in a group of CKD-5 patients on HD. Previous research had only examined the relationship between single field-tests of balance, such as one leg stands (Desmet et al., 2005), or composite scores of physical function including a balance element (Rossier et al., 2012; Wang et al., 2017; Kono et al., 2018) and falls in dialysis populations. These revealed a significant relationship for composite scores only (Wang et al., 2017; Kono et al., 2018).

Many CKD-related alterations may result in impaired postural balance in HD patients. First of all, muscle atrophy is very common in these patients and is one of the main factors potentially leading to impairments of postural control, due to reduced ability of the proximal and distal lower limb muscles to actively compensate the small perturbations of balance that occur continuously throughout the day (Horlings et al., 2009). Additionally, the extreme sedentary behaviour imposed by the dialysis treatment can lead to a general physical deconditioning that can also affect postural balance (Kiers et al., 2013). Thirdly, HD patients may also be affected by peripheral neuropathy as a consequence of advanced diabetes (the most common cause of CKD), elevated uraemia, and drug toxicity (Baluarte et al., 2017), which is also a well-established risk factor for impaired balance, since it affects directly the efferent component (e.g. motor nerves) of balance control (Hewston et al., 2016). Not surprisingly, previous research has shown that postural balance, assessed by means of force platforms, is significantly worse in HD patients than in healthy age-matched individuals (Blake et al., 2004; Shin et al., 2014; Magnard et al., 2014), however, ours is the first study to provide evidence of a significant association between postural balance and falls in this patient group.

Another interesting finding from our investigation is that velocity-based measures of balance (such as VelY) seemed to better discriminate fallers from non-fallers compared to position-based measures (e.g. RangeY), as highlighted in Chapter 6 (Table 6.1). This is in agreement with the findings of Magnard et al., (2014), who postulated that these kind of outcomes may be more useful in assessing balance and predicting falls in this patient population.

Overall, the interpretation of our study results on balance and falls leads us to confirm the already existing recommendation that exercise-based interventions aiming to reduce falls

should incorporate balance training (Sherrington et al., 2011) in HD patients also. Since postural balance was associated with increased odds of falling independently from frailty, and because a "loss of balance" was the second most commonly reported precipitating factor accompanying the falls (18.8% of falls) experienced by study participants, we are led to think that impaired postural balance may be an independent risk factor implicated in the aetiology of falls in the population of CKD-5 patients on HD.

7.2.3 Cardiovascular function and falls in HD patients

Cardiovascular function is a broad concept that involves the maintenance of the major functions of the cardiovascular system. One of the main functions is the homeostasis of fluid balance within the different body compartments. This is achieved by regulating HR, BP and peripheral resistance. In the context of cardiovascular disease, these mechanisms can be impaired and this can result in orthostatic hypotension and cardiovascular-mediated syncope, two known risk factors for falls (Finucane et al., 2017). We already know that community-dwelling older adults are at high risk of orthostatic hypotension and syncope-related falls due to the cardiovascular impairment resulting from the ageing process (Finucane et al., 2014; Jansen et al., 2015). Because the population of CKD-5 patients on HD is growing older (UKRR 2016), and CVD is the leading cause of death in these patients (USRDS, 2011; UKRR, 2016), we were inclined to hypothesise that a high number of falls may be due to impairment of cardiovascular function in people living with CKD-5. Therefore, one of the main objectives of this PhD thesis was to explore the relationship between cardiovascular function and falls in HD patients.

This possible relationship has not received much attention by previous research on HD and falls, as most studies have focused on the relationship between clinical characteristics or physical function/frailty and falls (Lopez-Soto et al., 2015). The only cardiovascular function factor that was consistently examined across studies was BP (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007; Abdel-Rahman et al., 2011; Polinder-Bos et al., 2014; Kono et al., 2018). These investigations reported contrasting results as to whether impaired BP regulation may contribute to falls. In particular, two studies found that low pre-dialysis SBP was associated with a higher number of falls (Cook et al., 2006) or time

to first fall event (Polinder-Bos et al., 2014). In addition, three other studies did not highlight any significant relationship between pre or post-dialysis BP and falls in logistic regression analysis (Desmet et al., 2005; Roberts et al., 2007; Abdel-Rahman et al., 2011). More importantly, only three studies examined the possible relationship between orthostatic decrements of BP and falls (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007). These investigations did not find any association between the BP response to an orthostatic challenge and falls via logistic regression analysis. However, all of these studies employed an orthostatic challenge consisting of an active stand with standard oscillometric BP measurements, an examination that is widely used in clinical settings for a time-efficient assessment of orthostatic intolerance symptoms but also subjected to standardisation issues of testing procedures (Cooke et al., 2009; Pasma et al., 2014).

Therefore, in Chapter 5 of this PhD thesis we sought to further explore the relationship between cardiovascular function and falls by performing a comprehensive assessment of haemodynamic function at rest, and in response to HUT-60°, using more advanced continuous beat-to-beat technology (Shaw et al., 2015). In addition, we also aimed to explore the relationship between baroreflex function, the main physiologic mechanism involved in the short-term regulation of haemodynamic variables in response to standing (Chapter 1, paragraph 1.2.4.3), and falling status in CKD-5 patients on HD.

7.2.3.1 Baroreflex function and falls

To the best of our knowledge, this is the first research project investigating the relationship between baroreflex function and falls in CKD-5 patients on HD. The cross-sectional study presented in Chapter 5 revealed that lower number of baroreceptor events, measured using the sequence method (La Rovere et al., 2008), were associated with increased odds of falling in univariate regression analysis (Table 5.3). More importantly, the negative binomial regression analysis performed in Chapter 6 showed that low number of baroreceptor events and BEI predicted a higher number of falls (Table 6.4). Therefore, the overall findings from this PhD thesis suggest that poor baroreflex function may be an important risk factor for falls in this clinical population.

Despite no previous studies reporting a possible association between baroreflex function and falls, the observations that impaired baroreflex control is associated with BP decrements in response to orthostasis (Mattace-Raso et al., 2007), and that these decrements can lead to falls in non-uraemic older adults (Heitterachi et al., 2002), would seem to indirectly suggest that impaired baroreflex may be a significant risk factor for falls in the general population. However, people living with CKD-5 have a significantly higher burden of cardiovascular comorbidities compared with community-dwelling older adults (Foley et al., 1997) which is responsible for the common impairment of baroreflex function in these patients, as observed by many studies conducted on dialysis patients (Hildreth et al., 2012). Therefore, it is possible that this factor may contribute more markedly to the aetiology of falling in the CKD-5 population compared to non-uraemic, age-matched individuals.

One interesting finding, emerging from both Chapters 5 and 6, was that BEI but not BRS was associated with an increased risk of falling. The BEI is a measure that describes how often the baroreflex is activated (Di Rienzo et al., 2001), contrary to the BRS which is linked to the gain/strength of baroreflex activation (Pinna et al., 2015). Therefore, we plausibly take the view that frequency, rather than intensity, of baroreflex activation may contribute predominantly to an increased risk of falling. Because many spontaneous fluctuations of BP manifest suddenly throughout the day, as a result of changes in body position or more or less prolonged periods of standing (Silvani et al., 2017), the baroreflex has to constantly adjust HR and peripheral resistance to maintain cardiac output. Thus, a reduced frequency of baroreflex activation (i.e. low BEI) would imply that sudden drops in BP are not coupled effectively with concomitant increases of HR, which may result in a suboptimal cerebral perfusion possibly leading to dizziness symptoms and, consequently, falls (Shaw et al., 2015). As reported in Chapter 5, the number of down-events and down-BEI were significantly lower in fallers compared to non-fallers (Table 5.1). In the sequence method, the "down" component of baroreflex activation is indicative of vagal withdrawal (Martin-Vazquez et al., 2010) because a down-event occurs when a drop in BP triggers an increase in HR arising from sympathetic activation. Because the number of down-events appeared to better discriminate fallers from non-fallers (Table

5.1), we are led to think that the "down" component of baroreflex, representing vagal withdrawal, may contribute primarily to an increased risk of falling.

It should also be acknowledged that the relationship between baroreflex function and falls may vary depending on the method of measurement employed to assess the baroreflex. In this PhD research, baroreflex function was assessed with the sequence method (Pinna et al., 2000), however other invasive and non-invasive methods have been used historically (Chapter 1, paragraph 1.2.4.4). The sequence method belongs to the class of non-invasive methods based on the spontaneous fluctuations of BP and HR. Pinna et al., (2015) synthesised the advantages and limitations of this method. The main advantages of this method are that 1) it conveys prognostic information comparable to the invasive methods (Pinna et al., 2000), 2) it is a low-cost, and time-efficient non-invasive assessment, and 3) it allows a lower estimation bias on BRS due to the strict constraints on ectopic beats. Therefore, in light of our study findings, baroreflex function assessed using this method may be a valuable screening tool to identify patients at high risk of falls. However, two limitations of this method need to be taken into consideration. First of all, the stringent restrictions imposed on the simultaneous change of BP and HR may result in lack of suitable baroreceptor sequences for the calculation of BRS. Secondly, the non-invasive measurements of BP were taken from the index or middle fingers: as encountered in our investigation (Chapter 5, paragraph 5.3.1), this measurement could be compromised in those individuals suffering from distal ischemia. Consequently, the combined effect of these two limitations is that this method is very often associated with a high failure rate (Pinna et al., 2015). As previously reported, these failure rates can be as high as 28% in people with history of myocardial infarction (Maestri et al., 2009). Because patients living with CKD-5 have a high burden of cardiovascular comorbidities, researchers should cautiously allow for a 30% failure rate in the calculation of baroreflex indices when designing research studies.

The findings on baroreflex function and falls arising from this PhD thesis have a potential translational impact that warrants further investigation, as previous research has reported on the efficacy of multiple interventions to improve baroreflex function in various populations. In particular, orthostatic training has recently been shown to be a viable

passive therapy to improve baroreflex indices in adults with recurrent syncope (Mitro et al., 2018), and it may represent a valuable rehabilitation strategy for HD patients also in light of the high prevalence of syncope in this clinical population (Roberts et al., 2003; Roberts et al., 2007). Moreover, some research has shown that transitioning to nocturnal HD treatment improved both BRS (Chan et al., 2005) and BEI (Chan et al., 2008) by lowering BP, peripheral resistance, and by improving distensibility of conduit vessels in dialysis patients. Finally, there is now increasing evidence that physical exercise can improve baroreflex function in various patient populations (Deley et al., 2009; Sato et al., 2010; Green et al., 2011; Straznicky et al., 2011; Ganesan et al., 2014) including HD patients (Petraki et al., 2008). The exercise interventions in these studies consisted of aerobic training mostly (Petraki et al., 2008; Deley et al., 2009; Straznicky et al., 2011; Ganesan et al., 2014), and therefore this exercise modality may be a useful component of rehabilitation programs aiming to reduce the occurrence of falls by improving baroreflex function.

7.2.3.2 Haemodynamic responses to orthostasis and falls

We hypothesised that worse haemodynamic responses to HUT-60° would be associated with an increased risk of falling in CKD-5 patients on HD. The findings from Chapter 5 of this PhD thesis were that decrements of OscBP in response to HUT-60° were significantly associated with increased odds of falling in univariate but not multivariate analysis (Table 5.3), while in Chapter 6, the OscDBP response predicted a higher number of falls in negative binomial regression analysis (Table 6.4). Moreover, fallers also tended to have larger decrements of OscSBP compared to non-fallers (Table 6.3), possibly indicating that the inclusion of a larger sample size may have resulted in a significant association between OscSBP decrements and number of falls sustained by study participants. Overall, the findings from both Chapter 5 and 6 suggest that the aetiology of the high number of falls experienced by HD patients might be associated with an impaired orthostatic response of BP.

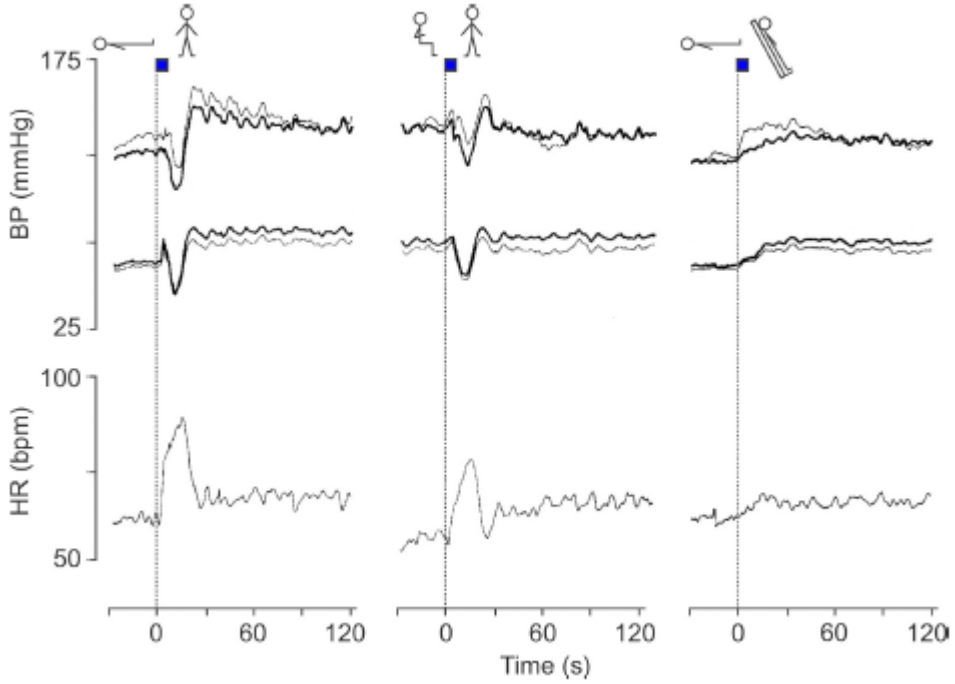
These results are in apparent disagreement with previous investigations that did not highlight any significant relationship between orthostatic changes of BP and falls in

dialysis populations (Desmet et al., 2005; Cook et al., 2006; Roberts et al., 2007). However, important methodological distinctions between these studies and our investigation are that 1) we employed a passive orthostatic challenge as opposed to an active stand, 2) the specific protocols of the active stand are not described in these studies, and 3) we computed the BP change from supine to HUT-60°, rather than measuring standing BP only (Roberts et al., 2007). Therefore, it is possible that merely the better standardisation of testing procedures in our study is responsible for the observed discrepancy. In addition, fallers had worse baroreflex function indices compared to non-fallers (Table 5.1), and therefore the emerging association between OscBP decrements to orthostasis and falls makes physiological sense since the baroreflex is the primary mechanism responsible for the short-lived responses of BP to orthostasis.

Although we also expected to observe a different orthostatic response of other haemodynamic variables (e.g. HR, SV, TPR, and contBP) in fallers compared to non-fallers, this was not confirmed (Table 5.2 and Table 6.3), and only CO was associated with a higher number of falls in univariate negative binomial regression (Table 6.4). This overall lack of response may be associated with the orthostatic challenge used in our study. Previous research has interestingly shown that, compared to active standing procedures, the initial response of contBP to passive tilting is less pronounced or even absent (Imholz et al., 1990; van Wijnen et al., 2017) (Figure 7.2). Consequently, all other concomitant haemodynamic responses may have not been triggered strongly enough due to the inadequate orthostatic challenge. Because all haemodynamic responses were recorded only over a short period (five minutes) of HUT-60°, it is possible that a longer duration of tilting might have elicited a more marked decrease of contBP and concomitant responses. Although previous research employing active stands did not find any relationship between orthostatic BP and falls (Desmet et al., 2005; Cook et al., 2006), it should be noted that these studies measured BP exclusively by means of intermittent sphygmomanometer assessments (protocols not described), and it cannot be excluded that continuous beat-to-beat measurements may have yielded different results. A recent literature review has suggested that an orthostatic challenge consisting of an active stand with contBP monitoring may be ideal to more accurately interpret the short term (first 180 seconds)

cardiovascular adjustments to orthostasis (van Wijnen et al., 2017). Moreover, this kind of assessment would be low-cost, time-efficient, and it would recreate real-world conditions, therefore it may have useful applications in clinical settings.

Figure 7.2. Typical response of contBP and HR to three orthostatic challenges. Active stand from supine position (left), active stand from sitting position (centre), and HUT (right) (van Wijnen et al., 2017, p.470).



Although we did not observe a significant relationship between contBP and an increased risk of falling, the finding that orthostatic decrements of OscBP were associated with participants' falling status (Chapter 5, Table 5.3), and predictive of a higher number of falls (Chapter 6, Table 6.4) has important translational implications. Particularly, these observations reinforce the evidence that simple OscBP measurements are generally considered adequate to evaluate the circulatory response to orthostasis (van Wijnen et al., 2017) and, in conjunction with a HUT-60° assessment, they may represent a valuable screening tool for practitioners to detect an increased risk of falling.

Because the findings from both Chapters 5 and 6 of this PhD thesis seem to suggest that orthostatic drops of BP are implicated in the aetiology of falling in CKD-5 patients on

HD, this raises the question of which interventions may be more suitable in reducing falls by improving this haemodynamic response. Even though many studies have now shown the benefits of physical exercise on baroreflex function (as described in paragraph 7.2.3.2), the question as to whether exercise programs can ameliorate the BP response to orthostasis requires careful examination. Some researchers have described a paradoxical relationship between exercise and orthostatic intolerance (van Lieshout, 2003) because aerobic training can improve orthostatic tolerance by increasing the plasma volume (Mtinangi et al., 1999; Wieling et al., 2002). However, trained individuals may have lower tolerance to orthostatic stress as a result of structural cardiac modifications that could lead to reduced stroke volume during prolonged standing (Levine et al., 1991). Nevertheless, CKD-5 patients on HD are known to be extremely inactive (Johansen et al., 2010) and, since marked sedentary behaviour is likely to negatively impact on orthostatic tolerance (Bonnin et al., 2001), they could benefit from exercise programs to improve the cardiovascular responses to orthostasis. Some authors have postulated that isotonic rather than isometric exercise may be advisable to minimise breathing patterns mimicking the Valsalva maneuver which could decrease the venous return and possibly result in brain hypoperfusion (Figueroa et al., 2010). Interestingly, there is also some evidence that orthostatic training (tilt training) may be beneficial in reducing the number of syncope-like events in healthy adults with history of syncope (Zeng et al., 2008). Because some research has shown that orthostatic training can also improve the orthostatic OscBP decrements (Sutcliffe et al., 2010), it may be a possible rehabilitation tool to reduce falls precipitated by orthostatic intolerance.

7.2.4 Diabetes and falls in HD patients

In Chapter 4 of this PhD thesis we observed that study participants classified as fallers were more likely to have diabetic nephropathy as PRD compared to non-fallers (34.9% vs 12.9%, p= 0.033). Moreover, diabetic nephropathy was also associated with increased odds of falling in logistic regression analysis (Table 4.5). A previous prospective cohort study conducted on a larger group of dialysis patients revealed that diabetes was an independent risk factor for falls in the study population (Desmet et al., 2005), and a recent

systematic review with meta-analysis concluded that diabetes is associated with an increased risk of falling in community-dwelling older adults (Yang et al., 2016). Therefore, we explored the confounding effect of diabetes on the study results in both Chapter 4 and 5 of this thesis.

Potentially, an advanced state of diabetes could have an adverse effect on falls via multiple pathways. For instance, falls may be precipitated by impaired physical function, due to the diabetes-related loss of muscle mass and strength (Park et al., 2007), or as a consequence of peripheral neuropathy which could negatively affect proprioception and postural balance (Hewston et al., 2016). In addition, advanced diabetes may negatively impact on cardiovascular function as a result of autonomic neuropathy (Vinik et al., 2018), which could impair the ability to regulate BP in response to orthostasis or during prolonged bouts of standing via the baroreflex. Moreover, diabetes may contribute to a higher risk of falls secondarily to impairments of vision, arising from retinopathy (Hewston et al., 2016), or as a consequence of hypoglycemia which may result from a high intensity treatment with insulin (Chiba et al., 2015). In addition, poor glycemic control with chronic hyperglycemia can trigger neurodegenerative processes potentially leading to cognitive impairment, which has been postulated to be one of the main risk factors for falls in people living with diabetes (Hewston et al., 2016).

While we did not find significant correlations between diabetes and physical function measures (with the only exception of low PA levels: Tables 4.7 & 4.8), diabetic nephropathy seemed to have an important mediating effect on the relationship between cardiovascular function and falls. In Chapter 5, we observed that adjusting the logistic regression analysis for diabetic nephropathy removed the significant associations between baroreflex function/haemodynamic responses to HUT-60° and falling status that were found in univariate stage (Table 5.3). In addition, diabetic patients had significant worse baroreflex function and orthostatic OscBP control compared to non-diabetics (Figures 5.1 & 5.2). Further analyses by means of point bivariate correlations revealed that no relationship between baroreflex/haemodynamic function and falling status persisted when patients with diabetic nephropathy were removed from the analysis. Therefore, we are led to think that, in CKD-5 patients on HD, diabetes may contribute to an increased risk of

falling predominantly via alterations of cardiovascular (e.g. autonomic neuropathy) rather than physical function (e.g. loss of muscle mass, or peripheral neuropathy).

Due to the fact that diabetic nephropathy is the main cause of CKD (UKRR, 2016), and that the prevalence of diabetes in CKD-5 patients is more than three times higher than in the general population (Guariguata et al., 2014), this comorbidity is likely to contribute to a high number of falls in this clinical population. Consequently, practitioners should consider implementing falls' risk screenings in those patients having diabetic nephropathy as PRD.

7.2.5 Impact of frailty and cardiovascular function on falls

Many recent systematic reviews have concluded that multiple risk factors such as older age, comorbidities, polypharmacy, and frailty or impaired physical function contribute to an increased risk of falling in the general population (Ambrose et al., 2013; Enderlin et al., 2015; Lusardi et al., 2017). In addition to these risk factors, CKD-5 patients on HD are characterised by severe CVD burden that often manifests with symptoms of orthostatic intolerance, impaired BP control and syncope, all of which may be implicated in the aetiology of falling. Therefore, one of the main objectives of this PhD research project was to explore the relative importance of frailty and cardiovascular function as potential exercise-modifiable risk factors for falls in the population of CKD-5 patients on HD. This research question was explored in the study presented in Chapter 6 of this PhD thesis.

In this study, we used a prospective design to explore the association between potential frailty and cardiovascular predictors, assessed at baseline, and the number of falls experienced by study participants during a 12-month follow-up. We hypothesised that 1) frailty/physical function and cardiovascular function (baroreflex function and haemodynamic responses to HUT-60°) would predict a higher number of falls, and 2) modelling the risk of falling by adding a cardiovascular function variable to a frailty-related variable only would improve the prediction of the number of falls sustained by study participants. The main findings from this study (as more fully discussed in paragraph 6.4) were that not only did cardiovascular function improve the prediction of falls, when combined with frailty (Figure 6.1), but it also showed a predominant contribution to the

number of falls experienced by study participants (Table 6.4). Moreover, this observation was also reinforced by the symptomatology described by fallers, who reported dizziness as most common precipitating factor leading to the falls experienced (41.3% of falls). The finding that baroreflex function and orthostatic decrements of blood pressure seemed to play a central role in the aetiology of falling is particularly important for a couple of reasons. First of all, we know that the high prevalence and incidence of CVD among CKD-5 patients on HD is responsible for multiple impairments of cardiovascular function such as, autonomic dysfunction, baroreflex impairment, BP dysregulation which could lead to many adverse clinical outcomes like recurrent hospitalisations, intradialytic hypotension, and sudden cardiac death (Kanbay et al., 2010; Di Lullo et al., 2016; Shafi et al., 2017; Mandel et al., 2017). Therefore, in addition to these common adverse outcomes, impairments of cardiovascular function may also constitute a CKD-specific risk factor for falls in this clinical population. Secondly, and more importantly, our findings challenge the current assumption that frailty is the factor primarily involved in the aetiology of falling in dialysis patients (McAdams-DeMarco et al., 2013; Kutner et al., 2014; Delgado et al., 2015). This second observation has noteworthy implications for potential preventive and rehabilitative interventions aimed to reduce falls in this patient group, since both baroreflex function and orthostatic BP decrements are modifiable risk factors. While the current rehabilitation approach to decrease the risk of falling in those individuals who may be at high risk, or who have already suffered a fall, recommends exercise programs to modify balance predominantly (Sherrington et al., 2011; Sherrington et al., 2017; Sherrington et al., 2019), the importance of aerobic training in reducing falls has not been emphasised. Current recommendations on falls prevention in the general elderly population tend to discourage exercise programs with a predominant walking component, as this kind of activity, and especially brisk walking, may expose those who are at high risk of falls already to a further risk (Sherrington et al., 2017). Although this is sensible advice, considering that many falls occur while walking (31.3% of falls in our study), our findings also suggest that some form of aerobic exercise may be beneficial in the prevention of falls. This is due to the fact that this type of exercise can positively impact on the baroreflex and orthostatic tolerance (Wieling et al., 2002; Petraki et al., 2008; Deley

et al., 2009). Moreover, some research has suggested that a simple gait training program on a treadmill may improve baroreflex function (Ganesan et al., 2014). Because a low number of daily steps predicted a higher number of falls in our study (Chapter 6, Table 6.4), we are further led to think that simply increasing the number of daily steps, by means of a low-cost walking program, may be effective in reducing the risk of falls (as previously postulated in paragraph 7.2.2.3). However, as highlighted by Sherrington et al., (2019), prescribing walking is not always possible, especially in those individuals whose physical deconditioning is so severe that a simple walking program would paradoxically result in an augmented risk of falling. For this reason, alternative exercise programs comprising a central aerobic component should be considered. For instance, a considerable amount of information relating to the clinical effectiveness and safety of intra-dialytic exercise programs is now available (Greenwood et al., 2014). In particular, an intradialytic exercise program consisting of cycling has been shown to improve baroreflex in a group of HD patients (Petraki et al., 2008). This exercise modality may be safer than brisk walking because it would not expose patients to an immediate risk of falling arising from stumbling, tripping or other environmental hazards, while increasing the levels of physical activity and improving baroreflex function.

7.3 Research limitations

As previously acknowledged in Chapters 4, 5 and 6, one of the main limitations of this PhD research project concerns the relatively low sample size. Although the patient sample achieved was reasonable to justify the statistical analyses performed (paragraph 2.1.3), a larger number of research participants would have increased the power of our observations and decreased the chances of committing a type II error. Particularly, the choice of covariates in our regression models was affected by the limited statistical power. Because only a small number of independent variables could be entered simultaneously in the logistic/negative binomial regression analysis, we used a data-driven approach to prioritise covariate selection. For instance, in Chapter 6 (paragraph 6.3.6) we adjusted the first multivariate stage of negative binomial regression analysis for antidepressant use and CRP, due to the fact that these factors were significantly different in fallers and non-fallers

(Table 3.1). However, it should be acknowledged that, when covariates are selected based on a data-driven approach, some genuine associations between risk factors and the dependent variable may be missed due to theoretical multicollinearity. For example, it could be speculated that since inflammation, and thus high CRP, has a mechanistic role in frailty (Walker et al., 2019), adjusting the analysis for CRP may cancel out the significant association between frailty and falls (Table 6.4). Nevertheless, in more detailed analysis, we did not observe statistical multicollinearity between CRP and frailty (r= -0.008, p= 0.947) and adjusting the negative binomial regression analysis for CRP only did not eliminate the significant association between frailty and falls (RR: 4.48, 95%CI: 1.71-11.70, p= 0.002). Ultimately, the possibility of studying a larger patient sample would have allowed us to design a more exhaustive statistical analysis with a priori, and theory-driven, selection of confounding variables. Moreover, due to the relatively high number of outcomes assessed, it should be acknowledged that some variables may have differed by chance between fallers and non-fallers.

Additionally, in Chapters 4 and 5, the categorisation into fallers and non-fallers was not exclusively based on the occurrence (or not) of falls recorded prospectively, as recommended by the Prevention of Falls Network Europe and Outcomes Consensus Group (Lamb et al., 2005). On the contrary, participants were also classified as fallers if they reported at least one fall in the previous 12 months. Although this decision was made to counterbalance the risk of misallocating patients with a significant history of falls in the non-fallers group, which would particularly bias the results of logistic regression analyses, it is well-known that recalling fall-related information in the previous 12 months is subject to misreporting (Hauer et al., 2006). Particularly, Ganz et al., (2005) estimated that recalling information on falls occurred in the past year has high specificity (91-95%) but relatively lower sensitivity (80-89%) compared to the criterion standard of prospective fall monitoring using fall diaries. Moreover, because the classification of fallers and non-fallers included a retrospective component (i.e. categorisation occurring prior to the assessment of potential risk factors), both Chapters 4 and 5 are classed as cross-sectional studies. Therefore, although these chapters provide an estimate of association between frailty/physical/cardiovascular function and falls, the cross-sectional design does not

allow to establish a possible causal relationship between these potential risk factors and the clinical outcome (i.e. falls).

Lastly, it should be acknowledged that the relationship between BP response to orthostasis and falls emerging from the study results remains somewhat unclear. While OscBP decrements to HUT-60° were significantly associated with increased risk of falling (Table 6.4), we did not find any association between contBP response to orthostasis and falls. This apparent discrepancy could simply be explained in light of the orthostatic challenge employed in this research project (HUT-60°). Although this passive orthostatic challenge has multiple benefits, such as easier standardisation of testing procedures and mitigation of skeletal muscle contraction effects on the baroreflex, a recent systematic review has pointed out that an active stand with concomitant contBP recording might be more suitable than HUT-60° to investigate the short-term cardiovascular responses to orthostasis (van Wijnen et al., 2017). Particularly, an active stand seems to trigger a more marked initial drop of contBP and concomitant haemodynamic responses, while the initial BP response to HUT-60° is often absent due to the slower transition to the upright position (van Wijnen et al., 2017). Therefore, it is possible that using an active orthostatic challenge might have been more useful than HUT-60° to interpret the relationship between BP response to orthostasis and falls.

7.4 Assessment of falls' risk in clinical research: further reflections

In addition to the study findings arising from Chapters 3, 4, 5 and 6, this PhD research project has also stimulated further reflections on the assessment of falls' risk in the context of clinical research that will be object of discussion in this section.

The investigation of falls as adverse clinical outcomes poses some unique challenges for researchers wishing to determine which risk factors are more likely to cause a fall in a specific population. As highlighted by a systematic review (Hauer et al., 2006), one of these challenges pertains to the operational definition of a fall. While the concept of falling is fairly intuitive for the lay public, in the context of clinical research, scientists should define what constitutes a fall or not as clearly as possible because different operational definitions may imply different aetiologies and prognostic relevance. For instance, some

researchers opted not to include those falls arising from an external force or a particular medical event, such as syncope, in the operational definition of a fall (Wang et al., 2017), with the rationale that these kind of fall events would be unavoidable, as opposed to those falls potentially linked to a more modifiable physiological mechanism. However, as pointed out by Hauer et al., (2006) such a strategy is at high risk of introducing a definitional artefact that may result in researcher bias, and therefore excluding falls deemed unavoidable should not be necessary. In agreement with most studies that investigated the risk of falling in HD patients (Desmet et al., 2005; Cook et al., 2006; Abdel-Rahman et al., 2011; Rossier et al., 2012; Kutner et al., 2014; Farragher et al., 2014; Polinder-Bos et al., 2014), we employed the operational definition given by Lamb et al., (2005) (i.e. "an unexpected event in which the participant comes to rest on the ground, floor, or lower level"). We used this definition as it minimises researcher bias, and is considered to be simple and reliably understandable by lay people (Hauer et al., 2006). Other studies have considered exclusively severe falls, such as fall-related fractures or injuries verifiable through medical care claims (Rossier et al., 2012; Delgado et al., 2015), while other investigations only focused on in-hospital falls (Lan et al., 2019). The main advantage of these studies is that falls operationalised in this manner can be easily reported, both prospectively and retrospectively, because the information is traceable via objectively documented medical records. Nevertheless, they only offer a restricted picture of the falls phenomenon, as only a small proportion of falls results in an injury requiring medical attention or fracture (Berry et al., 2008), while falls occurring in hospitalised patients may be due to primarily to an acutely altered physiological state (Oliver et al., 2010). Therefore, it is plausible that different risk factors may be implicated in the aetiology of these aggravated fall-events. Moreover, the estimates of falls emerging from these studies need to be interpreted carefully, as a direct comparison with the prevalence and incidence of generic falls is not possible.

Another common challenge encountered in clinical research aiming to investigate falls' risk is the well-known "recall bias", namely the possible error associated with recalling information on falls that may have occurred in a relatively distant time (Cummings et al., 2005). Not surprisingly, this bias affects mostly retrospective studies with a longer recall

interval (Ganz et al., 2005), but it can also manifest in studies with prospective design if falls are reported/documented infrequently (Hauer et al., 2006). A Cochrane review conducted by Gillespie et al., (2012) concluded that 29% of the studies included in their systematic review were classified at high risk of recall bias, making it the most common bias in clinical research investigating falls' risk. The Prevention of Falls Network Europe (ProFaNE) group suggested that, in order to minimise this bias, the most suitable method to ascertain falls should consist of daily diaries to be completed prospectively by the study participants and to be returned on a monthly basis for at least 12 months (Lamb et al., 2005). Moreover, there is now a general consensus that a study should be classified at high risk of recall bias if the method used to ascertain falls involves information self-reported by study participants at intervals longer than a month, or only at the end of the study (Gillespie et al., 2012). Therefore, according to the criteria proposed by Gillespie et al., (2012), the methodological approach used in this PhD research project should be classed at low risk of recall bias because information on falls was recorded prospectively by a researcher using a standardised diary at least once every month.

A further possible source of bias may occur during the recruitment process. It is well known that many observational studies aiming to identify risk factors for falls collect physical function data by means of various exercise-based assessments (Sherrington et al., 2019). This is done due to the fact that frailty and physical deconditioning are implicated in the aetiology of falling (Lusardi et al., 2017). Although highly frail people may be more prone to experience falls, they may also be more reluctant to engage in clinical research involving any kind of physical/exercise assessments due to physical activity avoidance behaviour (Delbaere et al., 2004). Consequently, the results emerging from these investigations may be influenced by the fact that a significant part of the population would not be able/willing to participate in the study.

In addition to the challenges listed above, we would like to highlight another issue relating to the nature of a fall as a clinical outcome in the context of falls' risk studies with prospective cohort design. In prospective cohort studies, participants are observed over time: researchers typically assess the potential risk factors and exposures at baseline, and ascertain the occurrence of clinical outcomes from the moment of study enrolment

onwards (Vandenbroucke et al., 2014). The main assumption of this study design is that all participants should be free from the clinical outcome of interest at the beginning of the study, and failing to ensure that this criterion is met would therefore constitute an overt violation of the study design. In studies assessing the risk of developing traditional adverse outcomes such as myocardial infarction, stroke, or cancer, the inclusion of patients who have suffered these outcomes before the actual enrolment in the study would be unilaterally highlighted as an example of bad science, and justly criticised by the medical research community. However, in the context of the assessment of falls risk, it is more difficult to ascertain whether or not patients are falls-free at the beginning of the study due to the fact that this clinical outcome is not routinely recorded by health care systems, unless the fall accident results in a fracture or another serious injury requiring some form of medical treatment. Consequently, researchers have often assumed artificially that all study participants were free from falls at the beginning of the study. In our opinion, this assumption introduces a high bias of group misallocation (i.e. patients wrongly classified as non-fallers) because it blindly implies that all those patients who remain falls-free for the whole duration of the prospective follow-up never suffered any falls in proximity of the study initiation. On the contrary, it is quite possible that individuals with a significant history of falls may not experience further falls from the moment of enrolment in the study, as a result of a complex interaction of environmental, behavioural, or physiological modifications (WHO, 2008). If researchers do not take any precautions to investigate the study participants' previous history of falls, then these individuals will be incorrectly classified as non-fallers. The repercussions of this misclassification would particularly affect those studies employing logistic regression analyses, where the dependent variable is dichotomised (i.e. falls: "yes" or "no"), and even more so if the sample size is relatively low. If the falling status cannot be ascertained beyond any reasonable doubt, a potential misclassification of fallers into non-fallers will drive the emerging association between potential risk factors and falls in the opposite direction, and would therefore significantly inflate the chances of committing a type II error.

To minimise this bias, we would encourage three main courses of actions when designing a prospective cohort study aiming to explore the risk of falling: 1) logistic regression

analysis may be used in studies with relatively limited sample size only if researchers can ensure that all participants are free from falls at the time of enrolment in the study. Ideally, the participants' history of falls should be documentable according to the principles outlined by Lamb et al., (2005) to minimise the "recall bias"; 2) In absence of this fundamental preliminary information, the risk of falling may be explored by analysing count data (i.e. number of falls) rather than falling status, using Poisson or negative binomial regression modelling. Such a methodological approach would be less subject to misclassification issues because the effect of one participant being falsely classified as a non-faller would not influence the estimate of association emerging from the analysis; 3) Logistic regression analysis may be used cautiously in large cohort studies regardless of the assumptions on participants' previous history of falls, as the high statistical power achieved in these studies is likely to override the risk of committing a type II error arising from misallocation.

In addition, some researchers also postulate that a time-to-event analysis using Cox regression may be preferable to logistic regression (Polinder-Bos et al., 2014) because some factors assessed at baseline can be subjected to more or less sudden changes, and therefore they would be more likely to contribute to the falls occurring closer to the time of assessment. Moreover, it should also be considered that a fall may result in a paradoxical latency period from further falls ascribable to a serious injury requiring prolonged bedridden recovery. From this perspective, a time-to-event analysis may be more appropriate for those studies investigating risk factors of severe falls or fall-related fractures, since the hospitalisation required for the treatment of these fall events could partially prevent the study participants to experience further falls. In contrast, Poisson or negative binomial regression models may be used reasonably for the analysis of predominantly non-injurious falls.

7.5 Future research perspectives

The U.S Preventive Services Task Force (USPSTF) has recently updated the recommendations on falls prevention in community-dwelling older adults (Grossman et al., 2018). This document concluded that exercise interventions have shown a moderate

to substantial benefit, and they should therefore be considered the primary recommendation to prevent falls in older people at high risk of falling. The USPSTF has also highlighted that, due to great heterogeneity of trials, it is difficult to pinpoint precisely what kind of exercise modalities may be more beneficial. However, the most common exercise components were balance, gait and functional training (17 trails), followed by resistance (13 trials), flexibility (8 trials), and endurance (5 trials) training (Grossman et al., 2018). The recommendations also included multifactorial interventions, consisting of initial assessments of potentially modifiable risk factors (vision, gait, balance, postural blood pressure, environment, medication, psychological health and cognition) followed by prescription of individualized interventions, although the net benefit of these programs was only classified as "small". In addition, the USPSTF recommended for the first time against vitamin D supplementation as a preventive measure for falls in those individuals who are not known to have vitamin D deficiencies or osteoporosis. Moreover, the document also pointed out that the level of evidence for single interventions such as environment modification, psychological interventions or medication management does not allow the USPSTF to make a recommendation in favour or against these programs at the moment (Grossman et al., 2018).

Several research findings from this PhD thesis have potential translational implications to expand the current evidence around falls prevention in the CKD-5 population. These translational implications and future research perspectives will be object of discussion in the next paragraphs (7.5.1 & 7.5.2). Moreover, some observations from this thesis raise additional research questions that also need to be investigated to obtain a fuller understanding of the falls' risk phenomenon in CKD-5 patients on HD. For instance, many studies including ours (Chapter 3, paragraph 3.4.2) have concluded that dialysis populations are at higher risk of falling compared to the non-uraemic, age-matched population (Lopez-Soto et al., 2015). However, there is still no current evidence synthesis as to what extent this falls' risk is higher compared to the general population. Consequently, a systematic review with meta-analysis of the pooled estimates of falls (i.e. prevalence and incidence) in the CKD-5 population on HD is needed to allow a direct

comparison of the falls' risk profile of these patients with the general or other clinical populations.

7.5.1 Frailty, physical function, and falls

While frailty seemed to be consistently associated with an increased risk of falling in this PhD research project, the relationship between single physical function measures and falls was less clear. Because lower performance in TUG was associated with a higher number of falls in univariate negative binomial regression analysis, a composite assessment of physical function encompassing this measure may be useful in detecting falls' risk and should be explored by further research. Moreover, additional observational studies would be required to pinpoint which single physical function outcomes may predict falls more accurately.

The observations that low PA was one of the frailty components more strongly associated with falling, and that a lower number of daily steps was associated with a greater number of falls have important implications for future preventive and rehabilitative strategies. As outlined earlier (paragraph 7.2.2.3), simple interventions consisting of a walking program have been successfully administered to dialysis patients, and proved able to ameliorate quality of life and physical function (Manfredini et al. 2017). Therefore, future research should seek to determine whether this kind of intervention can also reduce the rate of falls in this clinical population. However, researchers should also attempt to maximise safety when designing a walking program because, as highlighted by Sherrington et al., (2011), the activity of walking may expose patients to a transiently high risk of falls, and ultimately this kind of intervention may not be prescribed to highly frail individuals since the risks could outweigh the possible benefits. This last observation should also underline the importance of early intervention. Since dialysis initiation is associated with increased sedentary behaviour and progressive deterioration of physical function (Kurella-Tamura et al., 2009), patients should be encouraged to increase their PA levels through walking at the very early stages of CKD-5 (or even earlier), before the physical deconditioning becomes so severe that the simple action of walking could represent a substantial threat for falls. In this regard, some researchers have suggested that "pre-habilitation" may be

effective in delaying the deterioration of physical function and loss of independence (Sheshadri et al., 2017). A practical example of pre-habilitation may be training muscle strength and balance before starting a walking program. Particularly, since worse postural balance was associated with increased odds of falling (Table 4.5), future exercise trials should explore the efficacy of balance training, or other multidimensional exercise programs including a postural balance component, not only in reducing the risk of falling but also in maximising walking stability in this patient group.

7.5.2 Cardiovascular function and falls

One of the most interesting findings arising from this PhD thesis is that baroreflex function, as assessed through BEI, was associated with an increased risk of falling. Although a direct biological mechanism may exist between impaired baroreflex function and falls (Mattace-Raso et al., 2007), further research would be required to clarify the physiologic processes linking baroreflex control and falls. In particular, Hildreth et al., (2012) have postulated that baroreflex may be impaired via two main aetiological pathways in CKD patients. The first pathway involves vascular stiffness and/or calcification across multiple arterial sites which would impede the aortic arch and carotid sinuses baroreceptors to sense BP changes effectively. In alternative, the baroreflex impairment could be due to abnormalities in central processing of the baroreflex, or to dysfunction of the sympathetic or cardiac vagal efferent pathways. Because arterial stiffness was already found to be an independent risk factor for falls in community-dwelling elderly individuals (Wong et al., 2014), further research should be designed to explore the interrelationships among arterial pulse wave velocity, baroreflex function, and falls in CKD-5 patients on HD.

In addition, as already acknowledged in paragraph 7.2.3.2, future studies should also explore the relationship between the haemodynamic responses to an active stand and falls in this patient population, as this type of orthostatic challenge may provide a more marked drop of contBP and concomitant haemodynamic responses (van Wijnen et al., 2017). Moreover, alternative orthostatic challenges such as passive sit to stand (Shaw et al., 2015)

can be implemented for those patients whose mobility is too poor to perform an active stand satisfactorily.

Finally, from a preventive and rehabilitative perspective, future exercise trials aiming to reduce the rate of falls in HD patients should consider incorporating an aerobic component, as this kind of training has been proved useful in improving baroreflex function (Petraki et al., 2008; Deley et al., 2009; Ganesan et al., 2014). Moreover, aerobic training would also increase significantly the PA levels, thus counteracting a further risk factor for falls. We are led to think that an intra-dialytic exercise intervention consisting of cycling may be the most viable rehabilitation strategy as, in contrast to walking programs, it would not expose patients to an immediate increased risk of falling (Sherrington et al., 2011). Furthermore, the benefits of this type of training would be twofold as it would improve baroreflex function on one side (Petraki et al., 2008), and counteract the dialysis-related physical inactivity on the other. Alternative or complementary interventions may involve orthostatic training, as this type of therapy has been shown to improve both baroreflex function and the orthostatic response of BP (Sutcliffe et al., 2010; Mitro et al., 2018). In addition, it should also be acknowledged that submaximal resistance training (30%-80% of 1RM) has been shown to improve markers of cardiovascular health such as blood pressure, VO_2, and plasma triglycerides (Cornelissen et al., 2011). Because this exercise modality would also positively impact on bone and muscle health, it could represent a viable rehabilitation strategy to target multiple needs of HD patients. Moreover, combining traditional aerobic training with resistance exercise seems to have a positive synergistic effect on cardiac function in people affected by CVD (Zhang et al., 2018).

7.6 Conclusions

- Findings from this PhD research project further reinforce the evidence that CKD-5 patients undergoing HD therapy are a clinical population at high risk of falls. Both the prevalence of study participants experiencing at least one fall per annum (37.7%), and the incidence of falls (1.16 falls/person-year) were high and indicative of an increased risk of falling compared to the non-uraemic, age-

matched population. This was the first 12-month prospective investigation of the prevalence/incidence of falls in HD patients conducted in the UK.

- As expected, frailty seemed to contribute significantly to the elevated risk of falling, as the Fried's frailty phenotype was associated with both increased odds of falling and a greater number of falls experienced by participants during the 12-month follow-up. Although patients classified as fallers did not appear to differ substantially in physical function measures such as TUG and CSTS-5, nor in muscle strength measures, lower postural balance performance was associated with increased odds of falling and it may represent an additional exercise-modifiable risk factor for falls independent from frailty. Moreover, subjectively and objectively measured low levels of PA were also associated with an increased risk of falling. This observation reflects the well-known detrimental effects of sedentary behaviour on general health. Moreover, it also highlights the importance of early intervention to increase the PA levels in HD patients.
- In addition to frailty, measures of cardiovascular function were also associated with an increased risk of falling. Particularly, baroreflex function indices reflecting frequency of baroreflex activation (i.e. BEI and number of baroreceptor mediated sequences of coupled HR and BP), as well as the OscBP response to HUT-60° were associated with increased odds of falling and a greater number of falls. Therefore, we conclude that both of these factors may be implicated in the aetiology of falling in the context of CKD-5. Moreover, the high number of falls precipitated by dizziness (41.3% of falls) seemed to indirectly suggest that an impaired short-term regulation of BP might contribute to a high number of falls experienced by HD patients. Diabetic nephropathy as primary renal disease was also associated with an increased risk of falling and it may partially mediate the relationship between cardiovascular function and falls, due to multiple complications arising from advanced diabetes such as autonomic neuropathy.
- The results from this PhD thesis indicate that modelling the risk of falling by adding a cardiovascular function variable to a frailty-only model improves significantly the prediction of number of falls experienced by CKD-5 patients

undergoing HD. More importantly, baroreflex function and the BP response to a passive orthostatic challenge showed a greater relative importance than frailty in predicting falls in this patient group. To the best of our knowledge, this is a novel finding and it challenges the current assumption that traditional risk factors such as older age, comorbidity, polypharmacy, and frailty contribute primarily to the aetiology of falls in this clinical population.

- From a preventive and rehabilitative perspective, the sum of observations arising from this PhD research project suggest that, in agreement with the current exercise recommendations for the prevention of falls in the general geriatric population, exercise-based interventions should target balance training with a high priority. However, due to the high number of falls that were ascribable to a degree of cardiovascular dysregulation, exercise interventions should also incorporate an aerobic training component. Aerobic exercise would improve baroreflex function as well as increase the PA levels and it may represent a CKD-5 specific rehabilitation strategy to reduce the number of falls experienced by HD patients.

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Appendix I. West of Scotland REC 3 ethical approval.

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 3
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Mr Tobia Zanotto
School of Health Sciences
Queen Margaret University
Queen Margaret University Drive
Musselburgh
EH21 6UU

Date 18th June 2015
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail WOSREC3@ggc.scot.nhs.uk

Dear Mr Zanotto

Study title:	**"FRAILTY, CARDIOVASCULAR FUNCTION AND RISK OF FALLING AMONGST PATIENTS RECEIVING HAEMODIALYSIS"**
REC reference:	**15/WS/0079**
IRAS project ID:	**172633**

Thank you for responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Mrs Liz Jamieson, wosrec3@ggc.scot.nhs.uk. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		14 August 2014
GP/consultant information sheets or letters	2	12 June 2015
Letters of invitation to participant	1	23 March 2015
Non-validated questionnaire	1	23 March 2015
Other [Response to the REC's questions]		12 June 2015
Other [Letter of support from Dr Colin Petrie]		08 June 2015
Other [Certification of basic resuscitation training]		09 June 2015
Other [Data collection sheet]	1	12 June 2015
Other [8.Tilt table protocol and termination criteria]		
Participant consent form	2	12 June 2015
Participant information sheet (PIS)	2	12 June 2015
REC Application Form [REC_Form_31032015]		31 March 2015
Research protocol or project proposal	1	23 March 2015
Summary CV for Chief Investigator (CI)		
Summary CV for supervisor (student research)		15 January 2015
Validated questionnaire		
Validated questionnaire		
Validated questionnaire		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/WS/0079	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Liz Jamieson

Liz Jamieson
REC Manager
On behalf of Dr Adam Burnel, Chair

Enclosures:	*List of names and professions of members who were present at the meeting and those who submitted written comments* "After ethical review – guidance for researchers"
Copy to:	*Professor Thomas Mercer, Queen Margaret University* *Mr Raymond Hamill, R&D Department Monklands Hospital*

West of Scotland REC 3

Attendance at Sub-Committee of the REC meeting on 30 June 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Adam Burnel	Consultant Psychiatrist - Chair	Yes	
Dr Anne-Louise Cunnington	Consultant Geriatrician	Yes	
Mr Eoin MacGillivray	Retired Dentist - Vice Chair	Yes	
Mr Robert Paterson	Retired Lecturer - Lay Plus Member	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Abibat Adewumi	Co-ordinators Assistant

Appendix II. Monklands Hospital R&D ethical approval.

NHS Lanarkshire

Mr Tobia Zanotto
School of Health Sciences,
Queen Margaret University
Queen Margaret University Drive
Musselburgh
EH21 6UU

R&D Department
Corporate Services Building
Monklands Hospital
Monkscourt Avenue
AIRDRIE
ML6 0JS

Date 15.07.2013
Enquiries to Elizabeth McGonigal
R&D Facilitator
Direct Line 01236 712459
Email elizabeth.mcgonigal@lanarkshire.scot.nhs.uk

Dear Mr Zanotto,

Project title: FRAILTY, CARDIOVASCULAR FUNCTION AND RISK OF FALLING AMONGST PATIENTS RECEIVING HAEMODIALYSIS

R&D ID: L15030

I am writing to you as Chief Investigator of the above study to advise that R&D Management approval has been granted for the conduct of your study within NHS Lanarkshire as detailed below:

NAME	TITLE	ROLE	NHSL SITE TO WHICH APPROVAL APPLIES
Dr Illona Shilliday	Consultant	Principal Investigator	Monklands Hospital

For the study to be carried out you are subject to the following conditions:

Conditions

- You are required to comply with Good Clinical Practice, Ethics Guidelines, Health & Safety Act 1999 and the Data Protection Act 1998.
- The research is carried out in accordance with the Scottish Executive's Research Governance Framework for Health and Community Care (copy available via the Chief Scientist Office website: http://www.cso.scot.nhs.uk/ or the Research & Development Intranet site: http://firstport2/staff-support/research-and-development/default.aspx
- You must ensure that all confidential information is maintained in secure storage. You are further obligated under this agreement to report to the NHS Lanarkshire Data Protection Office and the Research & Development Office infringements, either by accident or otherwise, which constitutes a breach of confidentiality.

- Clinical trial agreements (if applicable), or any other agreements in relation to the study, have been signed off by all relevant signatories.
- You must contact the Lead Nation Coordinating Centre if/when the project is subject to any minor or substantial amendments so that these can be appropriately assessed, and approved, where necessary.
- You notify the R&D Department if any additional researchers become involved in the project within NHS Lanarkshire
- You notify the R&D Department when you have completed your research, or if you decide to terminate it prematurely.
- You must send brief annual reports followed by a final report and summary to the R&D office in hard copy and electronic formats as well as any publications.
- If the research involves any investigators who are not employed by NHS Lanarkshire, but who will be dealing with NHS Lanarkshire patients, there may be a requirement for an SCRO check and occupational health assessment. If this is the case then please contact the R&D Department to make arrangements for this to be undertaken and an honorary contract issued.

I trust these conditions are acceptable to you.

Yours sincerely,

Raymond Hamill – Corporate R&D Manager

cc.

NAME	TITLE	CONTACT ADDRESS	ROLE
Dr Ilona Shilliday	Consultant	Ilona.Shilliday@lanarkshire.scot.nhs.uk	Principal Investigator
Professor Thomas Mercer		TMercer@cmu.ac.uk	Sponsor Contact
Dr Colin Petrie	Consultant	Colin.Petrie@lanarkshire.scot.nhs.uk	Named Contact

Appendix III. Victoria Hospital R&D ethical approval.

Research & Development

Research & Education Centre, Queen Margaret Hospital, Whitefield Road, Dunfermline, KY12 0SU

NHS Fife

Mr Tobia Zanotto
Duke Street, 144/5
EDINBURGH
EH6 8HR

Date 11 April 2017
Our Ref

Enquiries to Aileen Yell
Telephone 01383 623623 Ext 20940
E-mail aileenyell@nhs.net
Website www.nhsfife.org

Dear Mr Zanotto

Letter of access for research
Project Title : Frailty and risk of falling in patients with dialysis dependent chronic kidney disease (CKD) 15/WS/0079

This letter confirms your right of access to conduct research through NHS Fife for the purpose and on the terms and conditions set out below. This right of access commences on 11 April 2017 and ends on 30 September 2018 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation.

The information supplied about your role in research at NHS Fife has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. You are considered to be a legal visitor to NHS Fife premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through NHS Fife, you will remain accountable to your employer Queen Margaret University, but you are required to follow the reasonable instructions of Dr Arthur Doyle in this NHS organisation or those given on her behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings. You must act in accordance with NHS Fife policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with NHS Fife in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS Fife premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

NHS
Fife

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. As from 26 July 2010, your HEI employer may initiate your Independent Safeguarding Authority (IISA) registration (where applicable), and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

NHS Fife will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Dr Amanda Wood
Assistant R&D Director

cc: lmitchell@qmu.ac.uk

Appendix IV. PIS.

PARTICIPANT INFORMATION SHEET

Study Title: ***"Risk of falling in haemodialysis"***

You are being invited to take part in the research study entitled as above. This study is being done in part fulfilment of a PhD. Before you agree to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information sheet carefully and discuss it with others if you wish. Please ask if you have any questions or are unclear about anything. Take time to consider your decision.

What is the purpose of the study?

The consequences of a fall can be huge, and include injury, a break to your bones, reduced mobility and function, and admissions to hospital. Patients undergoing dialysis have been found to experience a higher number of falls compared to the general population. This may be due to lots of various reasons.

This study aims to investigate the number of falls occurring in patients on haemodialysis and explore some of the main reasons why they are falling. This may then allow us to plan and develop appropriate treatment measures to try and reduce dialysis patients' risk of future falls.

Why have I been invited?

You have been invited as you are a patient on dialysis at the Renal Unit, Monklands Hospital. A maximum of 100 participants will be involved in this study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to participate in the study, the researcher will meet with you while you are on dialysis. He will explain the structure of the study, give you an opportunity to ask questions, make sure that you understand what is required of you and ask you to sign a consent form. You will be given a copy of the consent form to keep. Your GP will be notified of your participation in the study. The researcher will review your medical notes to verify any falls information you provide, and to gain details on your medical history, dialysis, and blood results.

You will be asked to attend one session lasting about 2 hours, on a non dialysis day, to perform a range of tests that aim to assess physical and cardiovascular function while performing physical activities that are commonly encountered during daily living. Before you attend for the assessments you would be advised not to drink/eat anything other than water for 2 hours before the scheduled time. Also, you would have to bring your reading glasses, any medications you may need, for example, if you have asthma bring your inhalers with you or a light snack if you have diabetes. This one-off assessment session encompasses:

- The completion of three questionnaires on your levels of physical activity, quality of life, and confidence in performing various daily activities;
- A passive standing-up test to assess how quickly your blood pressure and heart rate adjust to new levels, when you move from the lying down position to a standing up position. This test involves continuous measurement of blood pressure and heart rate using ECG and blood

pressure cuffs positioned around your arm on your finger and 3 electrodes on your chest to monitor your heart rhythm. You will be asked to lie down and rest for 20 minutes on a special bed that can be electronically brought up to an almost standing position. Your blood pressure, heart rate and other cardiac function measures will be continuously monitored. After 20 minutes of quiet resting you will be passively brought up to an almost standing position and will be asked to remain as still as possible and try not to squeeze your muscles for 5 minutes. You will be strapped in place with a velcro strap over the hips, in order to prevent you falling over.

- A non invasive assessment of arterial stiffness: a thin collar and a blood pressure cuff will be placed around your neck and the top of your leg respectively. Three blood pressure measurements will then be recorded while you lie supine.
- Hand and Leg strength assessment: You will be asked to squeeze a handheld device that measures your hand grip strength. You will have to repeat this 3 times. You will also be asked to sit on a chair and kick your leg forward against resistance in order to measure your thigh muscles' strength.
- Three physical functioning tests: we will assess how fast you walk along a 15 feet track and how quickly you rise up from a chair, walk 3 meters, turn around and walk back again to sit on the same chair. The last test will assess how quickly you can stand up and sit down on a chair five times.
- A balance test: you will be asked to stand still on a special platform for 30 seconds under three conditions (open eyes, closed eyes and counting backwards aloud).
- Lastly, you will be asked to wear a physical activity monitor for 5 consecutive days, in order to assess how physically active you are on your

daily life. This involves having a small device attached to your thigh that records your activity levels.

Following completion of baseline assessments you will then be monitored over the next year for any falls and will be asked to report in a weekly diary if you have fallen. Details will be taken on any falls experienced. This will be completed when you are at home. The researcher may also arrange periodic telephone calls with you to ask how you are doing, and if you have experienced any falls.

What are the possible disadvantages and risks of taking part?

There are no known serious disadvantages and risks of taking part in this study. It is recognised that asking for information on any falls you may have experienced may be upsetting for you and we will respect your wish not to reveal any information if you do not want to. All physical function tests, are designed to imitate activities of daily living and therefore the risk of a serious adverse event, such as for example a heart attack or a fall is not greater than the risk you are exposed to in your daily life when you perform tasks such as standing up from a chair, walking, or carrying a shopping bag.

There is a small risk of feeling tired and local muscle soreness, because you will be asked to perform a number of physical tasks within a 2 hour period, especially if you are not generally physically active in your daily life. However, muscle soreness during physical tasks that you are not accustomed to, is a normal body response and is temporary. It normally goes away after 48 hours.

You may also experience some dizziness, lightheadedness, faster heart beat and perhaps some physical discomfort during the transition from the supine to the upright position. There is also a very small possibility that you may faint or develop an abnormal heart beat during the passive transition from lying to standing. These side effects normally resolve by going back into the lying position. However, we

will terminate the test immediately upon request or if we notice any unusual responses of your blood pressure and heart rate. All tests involved in this study, are carefully chosen because they are proven to be safe with the large majority of elderly people and with people with chronic illnesses. In addition, your renal consultant will carefully review you medical history and ensure that you do not have any known conditions that may increase your risk of fainting and that you are free from any acute infections at the time of testing. We will also perform resting 12 lead ECG before you perform the passive stand to ensure you are free from any abnormal cardiac rhythms that may also increase your risk of fainting. All tests will be performed in a private room in the renal dialysis unit, so in the rare occasion you may become unwell, medical staff will be readily available to help you.

Should you wish to ask for more information, the contact details of the consultant nephrologist (Dr Shilliday) who is the clinical supervisor of this study can be found at the end of this document.

Expenses and payments

You will not be paid for taking part in this study. You may be provided with expenses to cover your travel costs.

Involvement of your General Practitioner (GP)

With your consent, your GP will be notified of your participation in the trial. You should also make other medical practitioners not involved in the study, but who may be treating you, aware of your participation in the trial.

What are the possible benefits of taking part?

While there will be no immediate benefits to you following participation; discussing any falls experiences you may have had over the last year may

highlight certain factors that can be reviewed by the renal team. The information collected from you may be used to help develop falls prevention interventions for dialysis patients and reduce their risk of future falls.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. Your medical notes will be reviewed by the researcher and renal consultant only. Data, relative to research purposes only, will be exclusively reviewed if you agree to take part and provide written consent. Any information about you will have your name removed so that you cannot be identified at any time during the research, or in the final results. This is in accordance with the Data Protection Act (1998). All data produced by the research will be stored for 5 years.

What if relevant new information becomes available?

If new information becomes available that might influence your decision to be in the study you will be provided with a new Participant Information Sheet and will be asked to sign a new consent form.

In the unlikely event that you lose capacity to consent during the study, you will be withdrawn from the study. Data up to the point of withdrawal will be used for participants who lose capacity to consent during the study.

What if I don't want to carry on with the study?

You are free to withdraw from the study at any time. If you wish to withdraw, please contact your research team so that they can discuss your concerns with you. Information which has already been collected may still be used. If you decide to withdraw at any time we will ask your consent to use all the data collected up until the time when you decided to leave the study.

What will happen to the results of the research study?

The results will be written up and analysed as part of the researcher's PhD dissertation. This will be completed by August 2017. The results may also be published in a physiotherapy related journal at a later date. If you indicate on the consent form, we will let you know when the results will be published externally and how you will be able to gain access.

What happens at the end of the study?

When the study is over, we will send you a summary of the results and will be happy to discuss this with you further if you wish. Your data will be anonymised and stored for 5 years to be used by researchers for scientific studies.

What if there is a problem?

If you have any difficulties or problems, we will discuss these with you and treat as necessary.

If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through Queen Margaret University who is acting as the research sponsor. The person to contact is:

Mrs Kim Gilchrist,
Head of research and knowledge exchange development unit,
Queen Margaret University,
Email: kgilchrist@qmu.ac.uk
Telephone: 01314740000 (ask for Kim Gilchrist when prompted).

Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written complaint to:

Mrs Melanie MacLean,
Patient Affairs Manager,
Monklands Hospital,
Email: Melanie.MacLean@lanarkshire.scot.nhs.uk
Telephone: 01236 713 065.

Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS Lanarkshire, but you may have to pay your legal costs.

Who has reviewed the study?

The Research Ethics Committee at Queen Margaret University, and the West of Scotland REC 3 have reviewed this study. Research and Development, NHS Lanarkshire have also reviewed.

The West of Scotland REC 3, which has responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of medical ethics.

It is a requirement that your records, be made available for scrutiny by monitors from Queen Margaret University and NHS Lanarkshire, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Who is organising and funding the research?

This research study is being organised and sponsored by Queen Margaret University. None of the staff involved in the study will receive any additional income as a result of performing the study.

Contact for further information

For further information, please contact:

Mr Tobia Zanotto (PI)
Address: School of Health Sciences, Queen Margaret University, Queen Margaret University Drive, Musselburgh, East Lothian, EH216UU.
Email: TZanotto@qmu.ac.uk
Telephone: 07899337941

Contact details of medical lead

For further information, please contact
Dr Ilona Shilliday, Consultant Nephrologist
Address: Monklands Hospital, Monkscourt Avenue, Airdrie, ML6 0JS
Email: Ilona.Shilliday@lanarkshire.scot.nhs.uk
Telephone: 01236713167

Independent contact

Mr Alan Sommerville, Renal nurse.
Address: Monklands Hospital, Monkscourt Avenue, Airdrie, ML6 0JS.
E-mail: Alan.Sommerville@lanarkshire.scot.nhs.uk

Thank you very much for taking the time to read this information and for considering to participate in this study.

Appendix V. Consent form.

Queen Margaret University
EDINBURGH

NHS Lanarkshire

"Risk of falling in haemodialysis"

INFORMED CONSENT FORM

Please INITIAL below

1.	I confirm that I have read and understand the Participant Information Sheet (Version 2_12 June 2015). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw from study treatment at any time, without giving any reason, and without my medical care or legal rights being affected.	
3.	I understand and agree to be followed up for up to 12 months as explained in the patients information sheet (Version 2_12 June 2015).	
4.	I understand and agree to undergo the Tilt Table Testing procedure, as described in the Participant Information Sheet (Version 2_12 June 2015).	
5.	I understand that relevant sections of my medical notes and data collected during the trial will be looked at, in confidence, by authorised individuals from the study team at Queen Margaret University and my NHS Trust. I give permission for these individuals to have access to my records.	
6.	I understand that even if I withdraw from the above study, the data collected from me up until that time will be used in analysing the results of the trial.	
7.	I understand that my anonymised data will be stored up to 5 years which may be used by researchers for scientific studies.	
8.	I agree to my GP being informed of my participation in the study.	
9.	I agree to take part in the above study.	

Signature of patient

& **PRINTED** name

Today's date: _____

Signature of person taking consent:

& **PRINTED** name:

Today's date: _____

Version 2_12 June 2015

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several blocks	☐ 1	☐ 2	☐ 3
i. Walking one block	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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(SF-36 Standard, US Version 1.0)

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2
b. Accomplished less than you would like	☐ 1	☐ 2
c. Were limited in the kind of work or other activities	☐ 1	☐ 2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2
b. Accomplished less than you would like	☐ 1	☐ 2
c. Did work or other activities less carefully than usual	☐ 1	☐ 2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Thank you for completing these questions!

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(SF-36 Standard, US Version 1.0)

Appendix VII. ActivPal instructions leaflet.

"Risk of falling in haemodialysis"

Dear Sir/Madam,

Thank you very much for agreeing to take part in this PhD research study.
With regard to the ActivPal Physical Activity Monitor, please ensure you remember the following points for a correct use:

- Remember to wear the device with its vertical axis always aligned with your thigh;
- The image displayed in the ActivPal monitor must always be upright;
- Remember to take the device off before you shower/take a bath;
- You can remove the device before you go to sleep;
- You can replace the adhesive tape/sticker whenever you feel it might come off. We recommend you replace the tape at least once a day.
- After the fifth day you can take the ActivPal off and return it to the Renal Unit when you're next in for dialysis.

Many thanks for your co-operation and help with this study.
If you have any questions or you need more information do not hesitate to contact me.
Yours faithfully,

Tobia Zanotto
PhD candidate,
School of Health Sciences,
Queen Margaret University,
Edinburgh,
TZanotto@qmu.ac.uk
07899337941

Appendix VIII. Short IPAQ questionnaire.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → *Skip to question 3*

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → *Skip to question 5*

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → *Skip to question 7*

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

Appendix IX. HUT-60° protocol.

Head-Up Tilt to 60 degrees (HUT-60°) protocol

1. The assessment room will be private, quiet, of adequate size for all equipment, well ventilated with a constant temperature of approximately 20-22°C and humidity < 60%.
2. The assessment room is located within the Monklands Hospital renal dialysis unit and has immediate access to resuscitation equipment and medical staff trained in immediate life support.
3. Participants will be asked to have a light meal about 2-3 hours before testing, and they will be asked not to smoke or to consume caffeine/alcohol for at least 2 hours before the appointment. They will also be asked to avoid unaccustomed physical exercise or vigorous exercise in the 24 hours preceding testing.
4. Participants will attend on a non-dialysis day, ideally one day post dialysis, on their usual medication only.
5. Upon arrival, patients will be connected to the TFM as per manual instructions and helped onto the tilt table and will be secured in place by straps around their thighs and feet. There is a foot platform where they can rest their feet whilst in the HUT position.
6. The TFM continuous blood pressure monitor will be kept at heart level throughout the measurement (as per manual instructions) in order to correct the hydrostatic effects of head-up tilting. The monitor will be fastened to the patient's forearm by means of a Velcro fastener, and the patient's arm will be supported by an arm sling that will secure the monitor at heart level during the HUT-60°.
7. Patients will be instructed not to talk or sleep during the procedure, and that they can request to stop at any point if they wish. Patients will also be asked

to remain as still as possible (avoid isometric muscular contractions) during the whole duration of the procedure

8. Following patient set up, patients rest horizontally for 10 minutes before baseline measurements are taken.
9. Baseline measurements in the supine position are taken for a further 5 min.
10. The Tilt table is then inclined with a smooth transition and all haemodynamic data is recorded (from the start of transition) for a period of 5 minutes on 60 degrees head up (60 degrees is the recommended tilt angle for activation of baroreflex), if no symptoms develop.
11. If symptoms develop during this 5 minute period (see Termination Criteria), the patient is immediately returned to the supine position and nature of symptoms recorded from a list.
12. Patients will then return to horizontal supine position and remain there for 5 minutes. During this period, all physiological data will continue to be recorded.
13. Patients will be supervised in the assessment area until all indices of cardiovascular function have stabilised to pre-testing levels.

Summary of patient time with TFM

	Time period (min)	**Action**
1.	10	Preparation/set up
2.	10	Rest period in the supine position
3.	5	Baseline measurements taken in the supine position
4.	5	Measurements taken whilst at 60 degrees HUT
5.	5	Return to supine position
6.		Supervised until all physiological measures return to baseline figures

Exclusion criteria for HUT

- Unable/refuses to provide informed consent
- <18 years or>90 years
- Non ambulatory or lower limb amputee without prosthesis
- Unstable on dialysis and medications treatment (e.g. volume overloaded or uncontrolled cardiac arrhythmias such as atrial fibrillation, severe AV blocks, SVTs)
- Unstable medical conditions (e.g. recent MI, or TIA, uncontrolled diabetes)
- Suspected or known aneurysm
- A known severe stenosis anywhere (e.g. heart valves, LV outflow obstruction, coronary or carotid or cerebrovascular artery stenosis)
- pregnancy

Test Termination Criteria

The test will be terminated and the patient will be laid flat immediately and alarm will be raised if any of the following occurs:

11. Induction of syncope or presyncope symptoms associated with marked hypotension or bradycardia or both (dizziness, palpitations, blurred vision, nausea, lightheadedness, headache)
12. Completion of planned duration of test
13. Patient distress or discomfort
14. Patient request
15. Acute malignant arrhythmia (AF, SVT, HR<40bpm)
16. SBP falls >80mmHg or falls rapidly
17. Substantial reductions in BP (SBP>20 mmHg and/or DBP>10mmHg) compared to their baseline values without compensatory changes in other heamodynamic variables (HR, peripheral vascular resistance, stroke volume, cardiac output). This is defined as orthostatic syncope, where there are no compensatory adjustments due to failure of sympathetic tone to increase.
18. HR rises to greater than 170/min
19. Chest pain
20. Asystole
21. Any other adverse/unexpected event develops

The test will be interrupted immediately if any of the above criteria develop and the participant will be returned to the supine position. Loss of consciousness will

be prevented by continuous monitoring of HR and BP and termination of the test when both start decreasing substantially, without any other observations of compensatory mechanisms. A tilt duration of 20- 45 minutes has become widely accepted within the literature. However, these studies aim to induce syncope and use results diagnostically. The aim of this study is to gain an index marker of BRS and so a timeframe of 5 minutes tilt will be used.

Appendix X. History of falls survey.

Participant ID: **Date of Assessment:**

History of Falls Questionnaire

Date and time of fall:	Details	Comments
Activities prior to falling:		
(1) Ambulation (2) Transferring (3) Running (4) Sports (5) Stairs/curb (6) Other	Examples: (please circle) Walking Turning Standing Bed Chair Toilet Car w/c Shower/ bath Exercising Dancing Cycling Reaching overhead Bending down	
Perceived causes:		
(1) Accident/environment (2) Collapse episode (3) Dizziness/vertigo (4) Balance/gait impairment (5) Other (6) Uncertain of cause	Examples (please circle) Slip Missed seat Bumped/pushed Slid off surface Furniture/equipment broke Passing out Legs gave way Dizziness Lightheaded Weakness Trip/stumble Quick movement Lost balance	
Environmental factors:		
(1) Wet surface/slippery footwear (2) Uneven surface/steps (3) External forces (4) Lay surface (5) Other (6) Uncertain	Examples (please circle) Steps of unequal height Indistinguishable surface colours Furniture/railing broke Something moved/bumped the patient Visual glasses Darkness/dimness Glare	
Where did the fall occur?		

(1) Inside the home (2) Inside a building but not at home (3) Outside	Examples (please circle) Footpath Kerb/gutter Steps Garden	
When did the fall occur?		
(1) A HD day before dialysis (2) A HD after dialysis (3) A non-HD day		
Fall-related injuries	Details	Comments
(1) Fracture (2) Head injury (3) Joint dislocation (4) Ligament sprain (5) Non specified joint injury (6) Laceration (7) Bruising (8) No injury		
Healthcare sought		
(1) GP (2) Accident & Emergency (3) Hospitalised (4) NHS24 (5) Dentist		

Falls Diary **"Risk of falling in haemodialysis"**

Definition of a Fall:
"An unexpected event in which the participants come to rest on the ground, floor, or lower level"

Month..... Year.....
(Please start a new form each month)

Name	*ID number*	*Date/Time*	*Place*	*Activity*	*Precipitating Factors (how you felt prior to the event)*	*Any Injury?*	*Action?*	*No falls in the last year?*

(Version 1_23 March 2015)

Appendix XI. Falls diary.

Appendix XII. Tinetti FES questionnaire.

Falls Efficacy Scale

Name:_____ Date:_____

On a scale from 1 to 10, with 1 being very confident and 10 being not confident at all, how confident are you that you do the following activities without falling?

Activity:	Score: 1 = very confident 10 = not confident at all
Take a bath or shower	
Reach into cabinets or closets	
Walk around the house	
Prepare meals not requiring carrying heavy or hot objects	
Get in and out of bed	
Answer the door or telephone	
Get in and out of a chair	
Getting dressed and undressed	
Personal grooming (i.e. washing your face)	
Getting on and off of the toilet	
Total Score	

A total score of greater than 70 indicates that the person has a fear of falling

Adapted from Tinetti et al (1990)

Appendix XIII. Leaflet pre-assessment.

"Risk of falling in haemodialysis"

Dear Sir/Madam,

Thank you very much for agreeing to take part in this PhD research study.
Before coming to the hospital for the assessment tests, please remember the following points, which help us standardise testing conditions across different individuals, but also for your own safety and comfort:

- Have a light meal at least 2 hours before your scheduled appointment for the assessments;

- Do not consume caffeine, or alcohol, or smoke in the 2 hours preceding the assessments;

- Avoid any strenuous exercise in the 24 hours before the assessment day;

- On the assessment day, remember to wear or bring with you comfortable clothes and shoes that you can change into, that are suitable for physical tasks such as walking;

- Remember to bring with you a list of your medications and any other medication that your doctor may have prescribed for occasional use, such as your GTN spray for chest pain, or inhalers if you have asthma. If you suffer from diabetes, please remember to bring with you the type of snack that you normally have if you experience low blood glucose symptoms and your own glucose meter device if you have one.

Many thanks for your co-operation and help with this study.
If you have any questions or you need more information do not hesitate to contact me.
Yours faithfully,

Tobia Zanotto
PhD candidate,
School of Health Sciences,
Queen Margaret University,
Edinburgh,
TZanotto@qmu.ac.uk
07899337941

Appendix XIV. Correlations among postural balance variables.

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Falls (yes/no)	1.000	.287*	.235*	.373**	.373**	.298*	.408**	.235*	.278*	.328**	.250*	.297*	.353**	.353**	.349**	.332**	.300*
2. RangeY in EO	.287*	1.000	.954**	0.153	0.153	0.006	.246*	.891**	.679**	.790**	.695**	.781**	.254*	.254*	0.115	.315**	.785**
3. RMSY in EO	.235*	.954**	1.000	0.090	0.090	-0.024	0.163	.891**	.652**	.737**	.664**	.736**	0.166	0.166	0.065	0.214	.751**
4. SP in EO	.373**	0.153	0.090	1.000	1.000**	.956**	.977**	0.162	0.206	0.076	0.203	0.058	.758**	.758**	.854**	.639**	0.146
5. AbsVel in EO	.373**	0.153	0.090	1.000**	1.000	.956**	.977**	0.162	0.206	0.076	0.203	0.058	.758**	.758**	.854**	.639**	0.146
6. VelX in EO	.298*	0.006	-0.024	.956**	.956**	1.000	.885**	0.075	0.127	-0.056	0.130	-0.061	.668**	.668**	.836**	.523**	0.046
7. VelY in EO	.408**	.246*	0.163	.977**	.977**	.885**	1.000	0.215	.275*	0.180	.266*	0.149	.794**	.794**	.831**	.707**	0.225
8. Area95 in EO	.235*	.891**	.891**	0.162	0.162	0.075	0.215	1.000	.788**	.711**	.805**	.736**	0.188	0.188	0.144	0.197	.826**
9. RangeX in EC	.278*	.679**	.652**	0.206	0.206	0.127	.275*	.788**	1.000	.777**	.968**	.744**	.435**	.435**	.376**	.444**	.920**
10. RangeY in EC	.328**	.790**	.737**	0.076	0.076	-0.056	0.180	.711**	.777**	1.000	.776**	.953**	.386**	.386**	0.182	.471**	.910**
11. RMSX in EC	.250*	.695**	.664**	0.203	0.203	0.130	.266*	.805**	.968**	.776**	1.000	.777**	.411**	.411**	.367**	.415**	.951**
12. RMSY in EC	.297*	.781**	.736**	0.058	0.058	-0.061	0.149	.736**	.744**	.953**	.777**	1.000	.362**	.362**	0.157	.434**	.926**
13. SP in EC	.353**	.254*	0.166	.758**	.758**	.668**	.794**	0.188	.435**	.386**	.411**	.362**	1.000	1.000**	.889**	.964**	.405**
14. AbsVel in EC	.353**	.254*	0.166	.758**	.758**	.668**	.794**	0.188	.435**	.386**	.411**	.362**	1.000**	1.000	.889**	.964**	.405**
15. VelX in EC	.349**	0.115	0.065	.854**	.854**	.836**	.831**	0.144	.376**	0.182	.367**	0.157	.889**	.889**	1.000	.759**	.284*
16. VelY in EC	.332**	.315**	0.214	.639**	.639**	.523**	.707**	0.197	.444**	.471**	.415**	.434**	.964**	.964**	.759**	1.000	.441**
17. Area95 in EC	.300*	.785**	.751**	0.146	0.146	0.046	0.225	.826**	.920**	.910**	.951**	.926**	.405**	.405**	.284*	.441**	1.000

Abbreviations: EO: eyes open; EC: eyes closed; RangeX: range of centre of pressure (COP) displacement along the medial-lateral (ML) axis; RangeY: range of COP displacement along the anterior-posterior (AP) axis; RMSX: root mean square displacement along the ML axis; RMSY: root mean square displacement along the AP axis; SP: sway path; AbsVel: absolute velocity; VelX: velocity along the ML axis; VelY: velocity along the AP axis; Area95: 95% confidence ellipse area; * indicates a significant correlation (p-value < .05); ** indicates a significant correlation (p-value < .01).

Appendix XV. Correlations among PA, strength, physical function, and postural balance in EO

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Range X in EO	1.000	.682**	.971**	.651**	0.215	0.169	.241*	.892**	-0.103	-0.086	-0.121	-0.074	-0.097	-0.004	-.300**	.400**	.323**
2. Range Y in EO	.682**	1.000	.669**	.954**	0.153	0.006	.246*	.891**	-0.141	-0.185	-0.209	-0.131	-0.127	-0.096	-.373**	.500**	.384**
3. RMSX in EO	.971**	.669**	1.000	.654**	0.207	0.171	0.224	.910**	-0.101	-0.053	-0.091	-0.039	-0.082	-0.004	-.256*	.361**	.315**
4. RMSY in EO	.651**	.954**	.654**	1.000	0.090	-0.024	0.163	.891**	-0.088	-0.102	-0.119	-0.081	-0.069	-0.124	-.306**	.424**	.352**
5. AbsVel in EO	0.215	0.153	0.207	0.090	1.000	.956**	.977**	0.162	-0.022	0.031	-0.010	0.113	-.477**	-.361**	-0.152	0.072	0.125
6. VelX in EO	0.169	0.006	0.171	-0.024	.956**	1.000	.885**	0.075	0.007	0.088	0.041	0.153	-.402**	-.339**	-0.062	-0.032	0.095
7. VelY in EO	.241*	.246*	0.224	0.163	.977**	.885**	1.000	0.215	-0.047	-0.006	-0.044	0.091	-.499**	-.376**	-.232*	0.159	0.167
8. Area95 in EO	.892**	.891**	.910**	.891**	0.162	0.075	0.215	1.000	-0.149	-0.102	-0.133	-0.066	-0.092	-0.059	-.308**	.439**	.377**
9. Time standing	-0.103	-0.141	-0.101	-0.088	-0.022	0.007	-0.047	-0.149	1.000	.341**	.310*	0.214	-0.123	-0.065	0.187	-0.070	-0.156
10. Time stepping	-0.086	-0.185	-0.053	-0.102	0.031	0.088	-0.006	-0.102	.341**	1.000	.986**	.631**	0.042	0.072	.473**	-.473**	-.399**
11. Daily steps	-0.121	-0.209	-0.091	-0.119	-0.010	0.041	-0.044	-0.133	.310*	.986**	1.000	.648**	0.071	0.083	.514**	-.522**	-.450**
12. Daily sit to stands	-0.074	-0.131	-0.039	-0.081	0.113	0.153	0.091	-0.066	0.214	.631**	.648**	1.000	0.104	0.029	.349**	-.376**	-.295*
13. Handgrip	-0.097	-0.127	-0.082	-0.069	-.477**	-.402**	-.499**	-0.092	-0.123	0.042	0.071	0.104	1.000	.592**	.364**	-.340**	-.343**
14.Leg extension	-0.004	-0.096	-0.004	-0.124	-.361**	-.339**	-.376**	-0.059	-0.065	0.072	0.083	0.029	.592**	1.000	.407**	-.353**	-.508**
15. Gait speed	-.300**	-.373**	-.256*	-.306**	-0.152	-0.062	-.232*	-.308**	0.187	.473**	.514**	.349**	.364**	.407**	1.000	-.900**	-.729**
16. TUG	.400**	.500**	.361**	.424**	0.072	-0.032	0.159	.439**	-0.070	-.473**	-.522**	-.376**	-.340**	-.353**	-.900**	1.000	.756**
17. CSTS-5	.323**	.384**	.315**	.352**	0.125	0.095	0.167	.377**	-0.156	-.399**	-.450**	-.295*	-.343**	-.508**	-.729**	.756**	1.000

Abbreviations: PA: physical activity; EO: eyes open; RangeX: range of centre of pressure (COP) displacement along the medial-lateral (ML) axis; RangeY: range of COP displacement along the anterior-posterior (AP) axis; RMSX: root mean square displacement along the ML axis; RMSY: root mean square displacement along the AP

axis; AbsVel: absolute velocity; VelX: velocity along the ML axis; VelY: velocity along the AP axis; Area95: 95% confidence ellipse area; TUG: timed up and go test; CSTS-5: 5 repetitions chair sit to stand test; * indicates a significant correlation (p-value < .05); ** indicates a significant correlation (p-value < .01).

Appendix XVI. Correlations among PA, strength, physical function, and postural balance in EC

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Range X in EC	1.000	.777**	.968**	.744**	.435**	.376**	.444**	.920**	-0.232	-0.166	-0.186	0.032	0.029	-0.006	-.259*	.349**	.289*
2. Range Y in EC	.777**	1.000	.776**	.953**	.386**	0.182	.471**	.910**	-.360**	-.319*	-.342**	-0.167	-0.027	-0.068	-.402**	.478**	.338**
3. RMSX in EC	.968**	.776**	1.000	.777**	.411**	.367**	.415**	.951**	-0.252	-0.212	-0.230	0.000	-0.015	-0.050	-.301**	.395**	.335**
4. RMSY in EC	.744**	.953**	.777**	1.000	.362**	0.157	.434**	.926**	-.279*	-0.254	-.280*	-0.134	-0.087	-0.118	-.376**	.451**	.319**
5. AbsVel in EC	.435**	.386**	.411**	.362**	1.000	.889**	.964**	.405**	-0.175	-0.044	-0.054	0.173	-.246*	-.234*	-0.187	0.102	0.129
6. VelX in EC	.376**	0.182	.367**	0.157	.889**	1.000	.759**	.284*	-0.130	0.034	0.011	0.244	-.250*	-.252*	-0.072	-0.023	0.097
7. VelY in EC	.444**	.471**	.415**	.434**	.964**	.759**	1.000	.441**	-0.191	-0.112	-0.118	0.131	-.239*	-0.217	-.259*	0.189	0.184
8. Area95 in EC	.920**	.910**	.951**	.926**	.405**	.284*	.441**	1.000	-.303*	-.259*	-.280*	-0.078	-0.049	-0.090	-.361**	.446**	.358**
9. Time standing	-0.232	-.360**	-0.252	-.279*	-0.175	-0.130	-0.191	-.303*	1.000	.341**	.310*	0.214	-0.123	-0.065	0.187	-0.070	-0.156
10. Time stepping	-0.166	-.319*	-0.212	-0.254	-0.044	0.034	-0.112	-.259*	.341**	1.000	.986**	.631**	0.042	0.072	.473**	-.473**	-.399**
11. Daily steps	-0.186	-.342**	-0.230	-.280*	-0.054	0.011	-0.118	-.280*	.310*	.986**	1.000	.648**	0.071	0.083	.514**	-.522**	-.450**
12. Daily sit to stands	0.032	-0.167	0.000	-0.134	0.173	0.244	0.131	-0.078	0.214	.631**	.648**	1.000	0.104	0.029	.349**	-.376**	-.295*
13. Handgrip	0.029	-0.027	-0.015	-0.087	-.246*	-.250*	-.239*	-0.049	-0.123	0.042	0.071	0.104	1.000	.592**	.364**	-.340**	-.343**
14.Leg extension	-0.006	-0.068	-0.050	-0.118	-.234*	-.252*	-0.217	-0.090	-0.065	0.072	0.083	0.029	.592**	1.000	.407**	-.353**	-.508**
15. Gait speed	-.259*	-.402**	-.301**	-.376**	-0.187	-0.072	-.259*	-.361**	0.187	.473**	.514**	.349**	.364**	.407**	1.000	-.900**	-.729**
16. TUG	.349**	.478**	.395**	.451**	0.102	-0.023	0.189	.446**	-0.070	-.473**	-.522**	-.376**	-.340**	-.353**	-.900**	1.000	.756**
17. CSTS-5	.289*	.338**	.335**	.319**	0.129	0.097	0.184	.358**	-0.156	-.399**	-.450**	-.295*	-.343**	-.508**	-.729**	.756**	1.000

Abbreviations: PA: physical activity; EC: eyes closed; RangeX: range of centre of pressure (COP) displacement along the medial-lateral (ML) axis; RangeY: range of COP displacement along the anterior-posterior (AP) axis; RMSX: root mean square displacement along the ML axis; RMSY: root mean square displacement along the AP

axis; AbsVel: absolute velocity; VelX: velocity along the ML axis; VelY: velocity along the AP axis; Area95: 95% confidence ellipse area; TUG: timed up and go test; CSTS-5: 5 repetitions chair sit to stand test; * indicates a significant correlation (p-value < .05); ** indicates a significant correlation (p-value < .01).

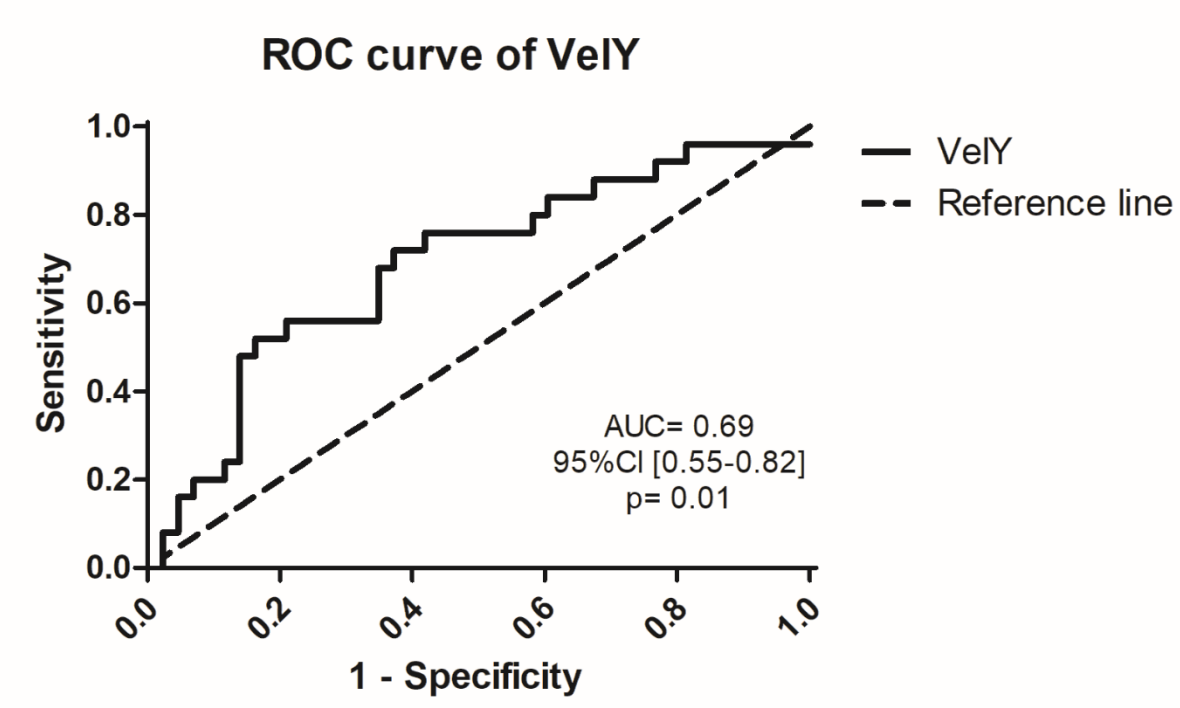
Appendix XVII. HRV and BPV characteristics of study participants.

Variables	All patients	Fallers	Non-fallers	P-value
Heart rate variability				
LFnu-RRI (%)	42.1±21.8	44.8±21.1	38.5±22.8	0.192
HFnu-RRI (%)	57.9±21.8	55.2±21.1	61.5±22.7	0.192
VLF-RRI (ms^2)	123.8±250.2	120.1±273.7	128.9±217.9	0.136
LF-RRI (ms^2)	119.7±342.8	135.5±437.7	97.5±125.8	0.143
HF-RRI (ms^2)	234.8±753.8	178.8±584.6	313.8±949.4	0.007
PSD-RRI (ms^2)	478.3±1175.6	434.4±1251.6	540.2±1079.6	0.040
LF/HF-RRI (1)	1.5±2.7	1.4±1.5	1.7±3.8	0.192
LF/HF (1)	0.9±1.9	08±0.5	1.2±2.9	0.271
Blood pressure variability - systolic				
LFnu-sBP (%)	29±13.1	26.8±11.3	31.7±15.1	0.126
HFnu-sBP (%)	29.3±17.7	32±19.7	24.9±13.6	0.132
VLF-sBP ($mmHg^2$)	6.2±16.3	4.8±7.3	8.3±23.8	0.424
LF-sBP ($mmHg^2$)	4.8±14.3	3±4.3	7.3±21.5	0.461
HF-sBP ($mmHg^2$)	3.6±10.6	2.7±2.8	4.9±16.1	0.790
PSD-sBP ($mmHg^2$)	14.5±40.6	10.4±12.6	20.5±61	0.515
LF/HF-sBP (1)	1.6±2.6	1.2±0.9	2.1±3.9	0.163
LF/HF (1)	0.9±2	0.7±0.6	1.2±3	0.995
Blood pressure variability - diastolic				
LFnu-dBP (%)	30.4±11.2	29.8±10.1	30.9±12.7	0.701
HFnu-dBP (%)	28.9±16.3	28.3±15.7	28.9±17.2	0.866
VLF-dBP ($mmHg^2$)	2.3±3.9	2.2±4	2.4±3.8	0.249
LF-dBP ($mmHg^2$)	1.5±1.8	1.4±1.9	1.7±1.7	0.126
HF-dBP ($mmHg^2$)	1.4±2.5	1.1±1.5	1.8±3.4	0.123
PSD-dBP ($mmHg^2$)	5.2±6.7	4.7±6.7	5.9±7	0.088
LF/HF-dBP (1)	1.6±1.5	1.5±1.2	1.6±1.9	0.926
LF/HF (1)	0.9±1.8	0.7±0.5	1.1±2.7	0.413

Abbreviations: LFnu-RRI: Normalized low frequency component of HRV; HFnu-RRI: Normalized high frequency component of HRV; VLF-RRI: Very low frequency

component of HRV; LF-RRI: Low frequency component of HRV; HF-RRI: High frequency component of HRV; PSD-RRI: Power spectral density of HRV; LF/HF-RRI: Low frequency/high frequency ratio of HRV; LF/HF: Low frequency-diastolic blood pressure/HF-RRI; LFnu-sBP: Normalized low frequency component of systolic BPV; HF-nu-sBP: Normalized high frequency component of systolic BPV; VLF-sBP: Very low frequency component of systolic BPV; LF-sBP: Low frequency component of systolic BPV; HF-sBP: High frequency component of systolic BPV; PSD-sBP: Power spectral density of systolic BPV; LF/HF-sBP: Low frequency/high frequency ratio of systolic BPV; LFnu-dBP: Normalized low frequency component of diastolic BPV; HF-nu-dBP: Normalized high frequency component of diastolic BPV; VLF-dBP: Very low frequency component of diastolic BPV; LF-dBP: Low frequency component of diastolic BPV; HF-dBP: High frequency component of diastolic BPV; PSD-dBP: Power spectral density of diastolic BPV; LF/HF-dBP: Low frequency/high frequency ratio of diastolic BPV.

Appendix XVIII. ROC curve analysis of VelY.



Appendix XIX. Research article (Chapter 5).

PLOS ONE

RESEARCH ARTICLE

Baroreflex function, haemodynamic responses to an orthostatic challenge, and falls in haemodialysis patients

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Abstract

Background

Stage 5 chronic kidney disease patients on haemodialysis (HD) often present with dizziness and pre-syncopal events as a result of the combined effect of HD therapy and cardiovascular disease. The dysregulation of blood pressure (BP) during orthostasis may be implicated in the aetiology of falls in these patients. Therefore, we explored the relationship between baroreflex function, the haemodynamic responses to a passive orthostatic challenge, and falls in HD patients.

Methods

Seventy-six HD patients were enrolled in this cross-sectional study. Participants were classified as "fallers" and "non-fallers" and completed a passive head up tilting to 60° (HUT-60') test on an automated tilt table. ECG signals, continuous and oscillometric BP measurements and impedance cardiography were recorded. The following variables were derived from these measurements: heart rate (HR) stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), number of baroreceptor events, and baroreceptor effectiveness index (BEI).

Results

The forty-four participants who were classified as fallers (57.9%) had a lower number of baroreceptor events (6.5±8.5 vs 14±16.7, p = .027) and BEI (20.8±24.2% vs 33.4±23.3%, p = .025). In addition, fallers experienced a significantly larger drop in systolic (-6.4±10.9 vs -0.4±7.7 mmHg, p = .011) and diastolic (-2.7±7.3 vs 1.8±6 mmHg, p = .027) oscillometric BP from supine to HUT-60' compared with non-fallers. None of the variables taken for the analysis were significantly associated with falls in multivariate logistic regression analysis.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

This cross-sectional comparison indicates that, at rest, HD patients with a positive history of falls present with a lower count of baroreceptor sequences and BEI.

Short-term BP regulation warrants further investigation as BP drops during a passive orthostatic challenge may be implicated in the aetiology of falls in HD.

Introduction

The World Health Organization (WHO) global report on falls prevention in older age [1] states that approximately 30% of people aged 65 years and older experience at least one fall every year, and nearly 50% of all injury-related hospital admissions are attributed to falls. Stage 5 chronic kidney disease (CKD-5) patients undergoing haemodialysis (HD) therapy have also been reported to have a higher risk of falling than the general population [2]. Prospective cohort studies of HD patients, with a 12-month follow-up, report that 26.3% [3] to 47% [4] experience at least one fall per annum. Patients who fell were observed to be at increased risk of adverse outcomes such as admission to nursing homes, higher number and duration of hospitalisations [3] and death [5].

A few prospective cohort studies have explored the association of potential clinical risk factors and falls in CKD-5 patients undergoing HD therapy with physical frailty primarily, older age, comorbidity, previous history of falls, and polypharmacy [2–4, 6] appearing to play a central role in the aetiology of falling. A recent review and summary of published evidence on falls in people with CKD, concluded that very few adequate quality studies in this area exist and many studies present with conflicting findings with regard to the importance of age, gender, different comorbidities, HD therapy and other physical frailty indicators, on the incidence and severity of falls in people with CKD-5 [7].

We already know that aging, history of falls and physical frailty are the most consistent risk factors that stand out from the rest, as predictors of future falls in the general geriatric and CKD population [7]. Moreover, cardiovascular disease (CVD) is the most prevalent comorbidity in the CKD population [8] and indices of poor cardiovascular function such as arterial stiffness [9], impaired blood pressure (BP) responses to a passive orthostatic challenge [10], and antihypertensive drug therapies [11, 12], have been linked to a higher prevalence or incidence of falls in elderly but otherwise healthy individuals. In two prospective cohort studies, a lower pre-dialysis systolic BP was found to be associated with falling status in a group of elderly dialysis patients [4, 13] suggesting that falls might be mediated by low BP spells in these patients. Other researchers suggested that autonomic failure and the significant fluid shifts associated with HD therapy might place HD patients at an increased risk of postural dizziness and hypotensive symptoms, possibly resulting in falls [14]. In addition, Cook et al., [4] reported that 31% of falls experienced by HD patients occurred during the transition from the seated to the upright position, suggesting that abnormal BP regulation, leading to dizziness spells, and potentially orthostatic hypotension (OH), may be implicated in the aetiology of falls in these patients. All these observations lead us to hypothesise that impaired BP regulation particularly during postural changes may be an additional risk factor for falls that further exacerbates the risks coming from physical frailty and chronological aging alone.

The baroreceptor reflex, or baroreflex, is the main physiological mechanism involved in the short-lived haemodynamic responses to change in body position, by regulating BP, heart rate, cardiac output, peripheral resistance, and thus preventing hypotension [15]. This mechanism

may be altered in CKD patients, and its impairment has been linked to vascular stiffness, increased cardiovascular risk and all-cause mortality in CKD patients [16, 17]. Despite the association of an impaired baroreflex control with the dysregulation of BP during orthostasis [18], which could lead to hypotensive symptoms and falls, the relationship between baroreflex function and falls in HD patients has been largely unexplored. Therefore, our study is the first step in the process of collecting and documenting evidence of potential relationships between falls and BP control during an orthostatic challenge.

The aims of this study were to explore the hypotheses that impaired baroreflex function would be associated with falls behaviour, amongst HD patients and that self-reported fallers would be more likely to have worse haemodynamic responses to an orthostatic challenge.

Materials and methods

Study design

An observational prospective study design was used to explore the relationship between baroreflex function and the falling status ("faller" vs "non-faller") in a group of prevalent HD patients.

Setting

The study was conducted in two Renal Units located in North Lanarkshire and Fife, United Kingdom, between October 2015 and August 2018. Recruitment started in October 2015 and continued on a rolling basis until December 2017. All baseline assessments were performed between October 2015 and December 2017, while the follow-up period ran from November 2015 to August 2018.

This research project abided by the ethical principles for medical research involving human subjects, as set out by the world medical association declaration of Helsinki, and received ethical approval by the West of Scotland NHS and Queen Margaret University Research Ethics Committees (NHS REC reference number: 15/WS/0079; ClinicalTrials.gov registration number: NCT02392299).

Participants

Ambulatory adult (>18 years) haemodialysis patients stable on HD therapy for at least 3 months fluent in spoken and written English were considered eligible to participate in the study.

Exclusion criteria were unstable dialysis and medication treatment, lower limb amputation without prosthesis, unstable cardiac condition, suspected or known aneurysm, clinically severe left ventricular outflow obstruction, critical mitral stenosis, critical proximal coronary artery stenosis, critical cerebrovascular stenosis, pregnancy and severe cognitive impairment.

Eligible patients were provided with a participant information sheet and were given seven days to consider whether to participate in the research project. All patients who agreed to take part provided written informed consent.

Standardisation of testing procedures

The assessment visit lasted about 2 hours, and occurred on a non-dialysis day, in order to minimise the influence of fluid and electrolyte shifts on data collected. Participants were instructed to follow standardised assessment protocol procedures that included no meals, caffeine or alcohol-containing drinks for at least 2 hours before the assessment, no smoking and no

unaccustomed physical exercise on the 24 hours preceding testing. No changes to medication prescription and timings were imposed.

Sociodemographic characteristics

Participant demographics (age, gender, height, weight, body mass index), and clinical characteristics (dialysis vintage, Charlson comorbidity index, medications and blood biochemistry data) were obtained from the patients' medical records. Height and weight were measured on the day of assessment.

Falls

A fall was operationally defined as an unexpected event in which the participant comes to rest on the ground, floor, or lower level [19]. The researcher (TZ) administered a falls questionnaire to all participants during dialysis, once a month, for a period of 12 months. The number of falls, circumstances, location, activities, precipitating factors, injuries, actions were documented for every fall. In addition, a history of falls questionnaire was completed by every participant at the baseline assessment visit. Participants were asked to report any falls they might have had in the previous 12 months. We defined as "faller" everyone who met at least one of these conditions: 1) at least one self-reported fall in the previous 12 months, and/or 2) at least one fall recorded by the researcher during the prospective follow-up period.

Haemodynamic and baroreflex function

The haemodynamic and baroreflex function was assessed at rest, in the supine position, and in response to a passive orthostatic challenge that involved head up tilting to 60 degrees from the supine position (HUT-60°).

For this measurement, the participants lay quietly awake in the supine position for 15 minutes [20], and were then tilted up for 5 minutes by means of an electrically controlled bed, followed by another 5 minutes of supine rest. The Task Force Monitor 3040i (CNSystems, Graz, Austria), was used for the non-invasive measurement of all hemodynamic data [21, 22, 23]. Stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were recorded by means of impedance cardiography (ICG). Heart rate (HR), R-R interval (RRI), and continuous BP (contBP) were measured by means of 6-lead electrocardiography (ECG) and continuous photoelectric plethysmography. The contBP was measured from the index or middle finger, based on which finger returned the best BP reading, by means of the unloading technique [24], and it was calibrated against oscillometric BP measurements. The hydrostatic effects of tilting were corrected by keeping the contBP monitor at heart level throughout the measurement, as per manual instructions. Oscillometric BP (oscBP) was measured with an electronically controlled sphygmomanometer connected to the participants' arm that was free from arteriovenous fistulas.

Baroreflex function was assessed by means of the baroreceptor effectiveness index (BEI), which represents how often the baroreflex produces a change in HR in response to a perturbation in BP [25]. The Task Force Monitor assesses the spontaneous activity of baroreceptors by using the sequence method which has been described to provide the equivalent prognostic information of the invasive methods used to measure the baroreflex [26].

The following variables were also derived and included in the analyses: i) blood pressure (BP) ramps defined as either an increase (up-ramp) or decrease (down-ramp) in contBP of at least 1 mmHg for 3 consecutive heart beats: "total-ramps" were defined as the sum of all down-ramps and up-ramps, ii) baroreceptor events, defined as the simultaneous coupling of a BP ramp with either an increase or decrease of the RRI of at least 4 ms. More precisely, a

"down-event" was classified as a concomitant decrease of continuous systolic BP (contSBP) and RRI of at least 1 mmHg and 4ms respectively, while an "up-event" was classified as a concomitant increase of contSBP and RRI of at least 1 mmHg and 4ms respectively. "Total-events" were classified as the sum of all down-events and up-events iii) The BEI was then computed as the ratio of occurred baroreceptor events and detected BP ramps expressed as a percentage. This index can be characterised by three components: the "down-BEI" that represents the ratio of occurred down-events and detected down-ramps, the "up-BEI" that represents the ratio of occurred up-events and detected up-ramps, and the "total-BEI" that represents the ratio of occurred total-events and detected total-ramps. In addition, the baroreflex sensitivity (BRS) was automatically computed by the Task Force Monitor software as the average slope of the regression lines between the RRIs and the contSBP values resulting from every baroreceptor event [27].

Statistical analysis

Statistical analyses were performed with SPSS (Version 23.0 for Windows, SPSS Inc., Chicago, IL). The Shapiro-Wilk Test (S-W) was used for the normal distribution checks of all data. Differences between fallers and non-fallers in demographic and clinical characteristics were analysed by means of a Chi-Squared test for categorical variables, and by either Mann-Whitney U or independent t-tests, as appropriate, for continuous variables: results are expressed as mean and standard deviation (SD).

The effect of grouping, i.e. fallers vs non-fallers, on the baroreflex and haemodynamic variables was analysed by means of either parametric (independent t-tests) or non-parametric (Mann-Whitney U) independent comparisons, based on normal distribution assumptions. Statistical limits for interpretation were set at an alpha level of $p = .05$.

The association between the baroreflex function/haemodynamic responses and falls (yes or no) was analysed by means of logistic regression analysis: variables reaching a statistical significance level of $p \leq 0.10$, in the preliminary independent comparisons, were entered in a univariate logistic regression model, which was adjusted a posteriori in a multivariate analysis. Statistical limits for interpretation of the logistic regression analysis were also set at an alpha level of $p = .05$.

Results

Recruitment and loss to follow-up

Three hundred and five patients undergoing outpatient HD therapy at the Renal Units were screened for eligibility by members of the renal team. Of these, 215 patients were deemed eligible to participate and therefore approached for recruitment and consenting. The recruitment rate was 35.3%, with 76 patients agreeing to participate in the study, and completing all baroreflex and haemodynamic measurements. Nine patients (11.8%) were lost to follow-up due to renal transplantation (n = 3; 3.9%) and death (n = 6; 7.9%), although 5 of these patients were retained in the data analysis due to their positive history of falls. Moreover, 14 patients were excluded from the baroreflex function data analysis due to atrial fibrillation (n = 7; 9.2%) and to poor circulatory blood flow to the fingers, which rendered the contBP measurement unusable (n = 7; 9.2%). This resulted in the inclusion of 62 patients in the baroreflex function analysis. After the exclusion of the 7 patients with poor blood circulation, 69 patients were retained for the haemodynamic responses analysis.

Sociodemographic characteristics

The demographic and clinical characteristics of patients are summarised in Table 1. Fallers were more likely to have diabetes as primary renal disease (PRD), and less likely to use diuretics compared to non-fallers.

Table 1. Sociodemographic and clinical characteristics of study participants (mean ± standard deviation).

Variables	All patients (76)	Fallers (44)	Non-fallers (32)	P-value
Sociodemographic characteristics				
Sex (% M)	53.9	52.3	58.1	0.620
Age (years)	61.1 ±14	59.9±13.2	62.3 ±15.2	0.482
Weight (Kg)	79.7 ±18.3	77.4±18.8	83.1 ±17.7	0.117
Height (cm)	165.8±8.7	166.4±9.7	165.3±7.2	0.595
BMI ($Kg^* m^{-2}$)	29±6.3	28±6.7	30.3±5.6	0.131
Clinical history				
Dialysis vintage (days)	726±716	755±777	666±633	0.780
CCI (score)	5.2±2.3	5.2±2.1	5.2±2.6	0.841
Primary renal disease (%)				
Diabetic nephropathy	26.7	34.9	12.9	0.033
Glomerulonephritis	18.7	18.6	19.4	0.935
Polycystic kidney	12	2.3	25.8	0.002
Renovascular or hypertensive	8	4.7	12.9	0.199
Other	18.7	20.9	16.1	0.603
Uncertain aetiology	17.3	18.6	12.9	0.512
Type of vascular access (%)				
Arteriovenous fistula	66.2	62.8	71	0.463
Central-venous	33.8	37.2	29	0.463
Inter-dialytic weight gain (Kg)	1.5±1.3	1.6±1.4	1.5±1.2	0.849
Prescribed medications				
Medications (n°)	11.8±3.7	12.3±3.8	11±3.7	0.106
Beta blockers use (%)	49.3	43.2	56.7	0.255
ACE-inhibitors use (%)	8	4.5	13.3	0.174
Ca-channel blockers use (%)	56	59.1	53.3	0.624
AngII-receptor antagonists use (%)	16	15.9	16.7	0.931
Alpha blockers use (%)	29.3	36.4	20	0.131
Antihypertensive use (%)	84	81.2	86.7	0.579
>1 antihypertensive use (%)	50	50	50	1.000
Opiates use (%)	20	15.9	26.7	0.258
Antidepressants use (%)	32	38.6	23.3	0.167
Diuretics use (%)	37.3	27.3	53.3	0.023
Laboratory values				
Hb (g/dL)	11.2±1.2	11.2±1.1	11.2±1.2	0.763
CRP (mg/L)	24.3±43.6	28.7±49.8	17.6±33.4	0.083
Bicarbonate (mmol/L)	21.2±3.2	21.4±3.3	20.8±3	0.455
Na (mmol/L)	139±2.8	138.7±3	139.4±2.5	0.728
K (mmol/L)	4.6±0.7	4.7±0.7	4.5±0.6	0.690
Urea (mg/dL)	16.3±5.1	16.2±5.9	16.4±4.1	0.859
Phosphate (mmol/L)	1.5±0.6	1.5±0.6	1.5±0.5	0.894
PTH (pmol/L)	27.5±31.3	27.3±34.2	27.9±27.9	0.859
Albumin (g/L)	37.1±4.2	36.8±4.5	37.5±3.8	0.435
Adjusted calcium (mmol/L)	2.3±0.1	2.3±.01	2.4±0.1	0.983
URR (%)	71.2±6	71.9±6.5	70.1±5.1	0.205
Kt/V	1.4±0.3	1.4±0.3	1.3±0.2	0.167

(Continued)

Table 1. (Continued)

Variables	All patients (76)	Fallers (44)	Non-fallers (32)	P-value
Creatinine (μmol/L)	634.3±159.9	617.4±173.7	654.6±139.6	0.326

Abbreviations: BMI: body mass index; CCI: Charlson comorbidity index; ACE: angiotensin-converting enzyme; Ca: calcium; AngII: angiotensin II; Hb: hemoglobin; CRP: C-reactive protein; Na: sodium; K: potassium; PTH: parathyroid hormone; URR: urea reduction ratio.

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Falls

During the 12-month follow-up, 26 of 72 patients (36.1%) experienced at least one fall, of which 14 (53.8%) experienced multiple falls. The maximum amount of falls experienced by one patient was 21. A total of 80 falls were recorded, resulting in an incidence of 1.11 falls/patient-year. In addition, 33 of 76 patients (43.4%) reported falling at least once in the previous 12 months and, overall, 44 of 76 patients (57.9%) reported either a fall in the previous year or during follow-up, and were therefore classified as fallers.

The most commonly reported factors perceived as a contributing cause of the falls experienced during follow-up were gait and balance issues (65.4%), environmental hazards (46.2%), and dizziness or syncope-like events (42.3%).

Haemodynamic and baroreflex function

The differences between fallers and non-fallers in all baroreflex variables are summarised in Table 2. At rest, fallers had a statistically significant lower count of baroreceptor "down-events" and "total-events", which also resulted in a significant lower "down-BEI" and "total-BEI", compared to non-fallers. In addition, the "up-BEI" during HUT-60' was also significantly lower in fallers. No significant differences in BRS were detected between the two groups.

The haemodynamic variables of fallers and non-fallers, in the supine position and during HUT-60', are described in Table 3. The differences in SV, CO, TPR, HR, contSBP, contDBP,

Table 2. Baroreflex function: Differences between fallers and non-fallers (mean ± standard deviation). Group means reflect averaged data for the total duration of 5 minutes in each postural position.

	Supine		HUT-60	
Variables	Fallers	Non-fallers	Fallers	Non-fallers
Up-ramps (n')	20.6±21	19.5±13.5	23.2±15.9	17.8±13.5
Down-ramps (n')	18.9±17.7	17.4±11.9	22.3±14.2	16.6±12.9
Total-ramps (n')	39.5±38.2	36.8±25	45.5±29.2	34.5±26
Up-events (n')	3.1±4	6.8±9.5	2.3±3.5	3.6±4.4
Down-events (n')	3.4±4.8*	7.1±7.8	3±3.6	3.9±4.5
Total-events (n')	6.5±8.5*	14±16.7	5.2±6.3	7.5±8.4
Up-BEI (%)	15.5±20.1	29.2±29.4	10.7±13.6*	19±15.7
Down-BEI (%)	23.3±27*	36.6±22.8	13.5±15.7	19.2±15.7
Total-BEI (%)	20.8±24.2*	33.4±23.3	12.6±13.4	19.1±13.2
BRS (ms/mmHg)	9.2±8.3	10±6.1	6.8±4.9	9.8±8.3

Abbreviations: HUT-60: head-up tilt at 60°; Up-BEI: up-events baroreceptor effectiveness index; Down-BEI: down-events baroreceptor effectiveness index; Total-BEI: total-events baroreceptor effectiveness index; BRS: baroreflex sensitivity

* indicates a statistical significant difference between groups ($p < .05$).

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Table 3. Haemodynamic variables: Differences between fallers and non-fallers (mean ± standard deviation).

	Supine		HUT60		ΔSupine-HUT60	
	Fallers	Non-fallers	Fallers	Non-fallers	Fallers	Non-fallers
RRI (ms)	869.2±134.1	926.6±187.5	809.4±168	868.4±192.8	-57.9±70.2	-58.1±64.5
HR (bpm)	70.9±10.7	67.7±13.2	77.7±15.2	72.9±15.2	6.6±8.3	5.5±5.8
contSBP (mmHg)	125.4±23.5	122±21.6	126.6±21.8	125.1±20.3	3.5±15.6	3±8
contDBP (mmHg)	76.5±14	79.4±16.4	82±15.2	85.4±16.3	6.1±10.2	6±7.6
contmBP (mmHg)	97.3±10.3	97±18.3	100.8±17.7	101.9±17.9	4.7±12.1	4.9±7.3
SV (ml)	63.6±14	69.1±16.1	59.1±11.8	62.9±15.5	-4.1±12.9	-6.2±16.3
CO (L/min)	4.5±1.1	4.7±1.5	4.5±0.9	4.5±1.2	0.03±0.9	-0.2±1.2
TPR (dyne*s/cm^5)	1731.8±432.4	1763.9±610.8	1797.7±451.5	1919.5±583.1	77.9±347.2	155.5±416.4
SI (ml/m^2)	34.8±8.3	37±10.7	32.4±7.4	33.4±8.5	-2.2±7	-3.7±9.1
CI (L/min*m^{-2})	2.5±0.7	2.5±1	2.5±0.5	2.4±0.7	0.01±0.5	-0.1±0.6
TPRI(dyne*s*m^2/cm^5)	3168.5±789.6	3381.1±1340.9	3292.1±806.8	3645.1±1259.6	146.7±624	264.1±773.5
TFC (1/kOhm)	32.3±10.6	34.4±11.1	30.3±10.1	32.4±11.1	-1.6±1.7	-2±1.8
OscSBP (mmHg)	131.3±22.6	124.1±19.8	122.2±18.3	123.9±13.1	-6.4±10.9*	-0.4±7.7
OscDBP (mmHg)	81.9±12.9	79.9±15.8	79.1±13.2	81.6±17.4	-2.7±7.3*	1.8±6

Abbreviations: HUT60: head-up tilt at 60°; RRI: R-R interval; HR: heart rate; contSBP: continuous systolic blood pressure; contDBP: continuous diastolic blood pressure; contmBP: continuous mean blood pressure; SV: stroke volume; CO: cardiac output; TPR: total peripheral resistance; SI: stroke index; CI: cardiac index; TPRI: total peripheral resistance index; TFC: thoracic fluid content; OscSBP: oscillometric systolic blood pressure; OscDBP: oscillometric diastolic blood pressure; ΔSupine-HUT60 represents the difference between the variables averaged over 5 minutes of HUT-60° and the variables averaged over 5 minutes of supine recording

* indicates a statistical significant difference between groups ($p < .05$).

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OscSBP, and OscDBP from the supine position to HUT-60° are expressed as absolute values. A significant larger decrement of OscSBP and OscDBP from supine to HUT-60° was detected between fallers and non-fallers, while no differences in the remaining haemodynamic variables were found.

Factors associated with falls

In univariate logistic regression, diabetic nephropathy, number of "down-events" and "total-events" in the supine position, "up-BEI" in the supine position, "up-BEI" in HUT-60°, OscSBP and OscDBP difference from the supine position to HUT-60° were associated with increased odds of falling (Table 4).

The univariate analysis was adjusted for diabetic status, as we retrospectively identified this factor to be potentially a significant confounder of the study results (Table 1). In this multivariate logistic regression model, none of the variables were significantly associated with falling (Table 4).

Further analyses

In order to evaluate the weight of the confounding effect of diabetes on the study results, we compared diabetic vs non-diabetic patients in terms of baroreflex function and BP response to HUT-60°. The independent comparisons between the two groups indicate that these variables were markedly decreased in diabetic patients (Figs 1 and 2).

In addition, we also performed a point biserial correlation analysis in the sub-group of non-diabetic patients (N = 44) to explore the relationship between the factors entered in logistic regression analysis and falls. No significant correlations were found for any of the baroreflex

Table 4. Logistic regression analysis: Factors associated with falls.

	Univariate		Adjusted	
Factors	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Clinical characteristics				
Diabetic nephropathy (%)	3.616 (1.064–12.286)	0.039	-	-
Baroreflex function				
Down-events supine (n')	0.909 (0.832–0.993)	0.034	0.932 (0.851–1.021)	0.130
Total-events supine (n')	0.953 (0.910–0.997)	0.037	0.961 (0.919–1.006)	0.087
Up-BEI supine (%)	0.977 (0.956–0.999)	0.045	0.978 (0.954–1.001)	0.066
Up-BEI HUT-60 (%)	0.961 (0.925–1.000)	0.048	0.975 (0.936–1.015)	0.221
Down-BEI supine (%)	0.980 (0.959–1.001)	0.058	0.986 (0.964–1.008)	0.216
Total-BEI supine (%)	0.978 (0.956–1.001)	0.060	0.983 (0.960–1.008)	0.175
Total-BEI HUT-60 (%)	0.964 (0.925–1.005)	0.085	0.983 (0.940–1.027)	0.437
Haemodynamic variables				
OscSBP Δsupine–HUT60 (mmHg)	0.930 (0.871–0.992)	0.028	0.939 (0.876–1.008)	0.080
OscDBP Δsupine–HUT60 (mmHg)	0.894 (0.813–0.983)	0.021	0.908 (0.816–1.010)	0.075

Abbreviations: CI: confidence interval; Up-BEI: up-events baroreceptor effectiveness index; Down-BEI: down-events baroreceptor effectiveness index; Total-BEI: total-events baroreceptor effectiveness index; HUT 60: head-up tilt at 60°; OscSBP: oscillometric systolic blood pressure; OscDBP: oscillometric diastolic blood pressure; Δsupine-HUT60 represents the difference between the variables averaged over 5 minutes of HUT-60' and the variables averaged over 5 minutes of supine recording.

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function/haemodynamic variables and falls ($-0.223 \leq R_s \leq -0.088$; $0.151 \leq$P-values≤ 0.583) when diabetic patients were removed.

The heart rate variability (HRV) characteristics of the study participants are also summarised in S1 Table.

Discussion

We hypothesised that HD patients classified as fallers would have worse baroreflex function than patients free from falls. In addition, we hypothesised that patients with falls would have worse haemodynamic responses to an orthostatic challenge.

We found that at rest, fallers had lower counts of baroreceptor "down-events" and "total-events", as well as a lower down-BEI and total-BEI compared to non-fallers. Although we also expected to see a significantly impaired ability to effectively regulate the haemodynamic variables via the arterial baroreflex mechanism in the fallers group, in response to a passive orthostatic challenge, this was not confirmed. However, we noted a significantly larger drop in OscBP during the transition from supine to HUT-60° which warrants further investigation.

Our findings on baroreflex function suggest that a lower number of baroreceptor sequences might discriminate patients with falls from those who are falls-free. Although no differences in the baroreflex slope, as assessed by BRS, were detected between fallers and non-fallers, measures reflecting how often the baroreflex is activated, such as the number of "down-events" and the "total-events", among other BEI indices, were significantly lower in the group of fallers. Interestingly, in resting conditions, the baroreceptor down-regulation seemed to better discriminate fallers from non-fallers. A baroreceptor down-event occurs when a systolic BP drop is coupled with a concomitant decrease of the RRI, namely an increase in HR. This is a physiologic response to a spontaneous perturbation of BP, which allows the maintenance of haemodynamic homeostasis [15]. Therefore, the lower count of baroreceptor "down-events" observed in fallers, as well as the lower "down-BEI" might indicate a relationship between the failure to increase HR in response to a spontaneous drop in BP and falls.

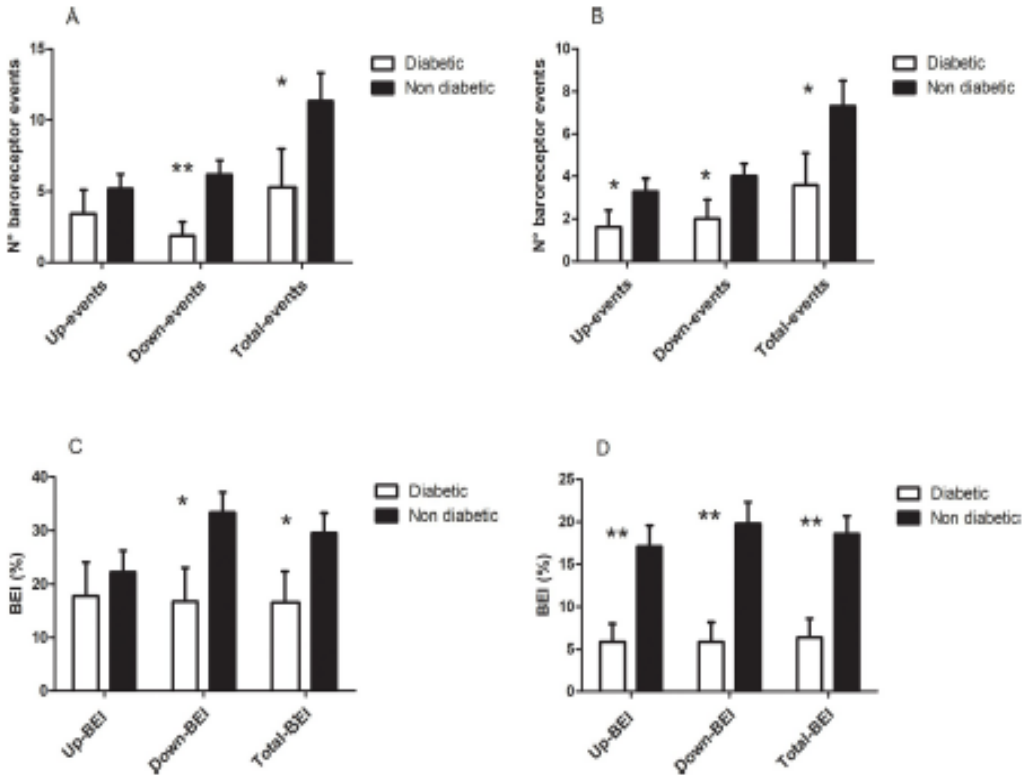

Fig 1. Baroreflex function in diabetic vs non-diabetic patients. Fig 1A shows the number of baroreceptor events in the supine position; Fig 1B shows the number of baroreceptor events in HUT-60'; Fig 1C shows the baroreceptor effectiveness index (BEI) in the supine position; Fig 1D shows the BEI in HUT-60'. * indicates a statistically significant difference ($p < .05$). ** indicates a statistically significant difference ($p < .01$).

https://doi.org/10.1371/journal.pone.0208127.g001

It should also be noted that, even though we did not assess a control group of healthy participants, the BEI indices measured in our patients (20.8±24.2% in fallers, and 33.4±23.3% in non-fallers) are considerably lower than the average 58±20% BEI measured in healthy individuals [27], while their BRS values were only slightly inferior (-15% to -25%) to those of an age-matched healthy population [28]. Because a reduced BEI has already been shown to be an independent predictor of all-cause mortality in patients with CKD [17], it is possible that this index might predict other adverse outcomes such as falls in this population. Potentially, the lower BEI as well as the lower number of baroreceptor events could be linked to syncope-related falls due to an impaired homeostasis of the HR and BP responses, which may lead to cerebral hypoperfusion with sudden onset of dizziness and pre-syncopal symptoms, which are commonplace among HD patients [14]. Interestingly, in the current study, almost half of the patients who experienced falls during the prospective observational follow-ups (42.3%) reported dizziness or syncope-like events as one of the symptoms preceding a falling event, which indirectly implicates this mechanism in the aetiology of falls in HD patients.

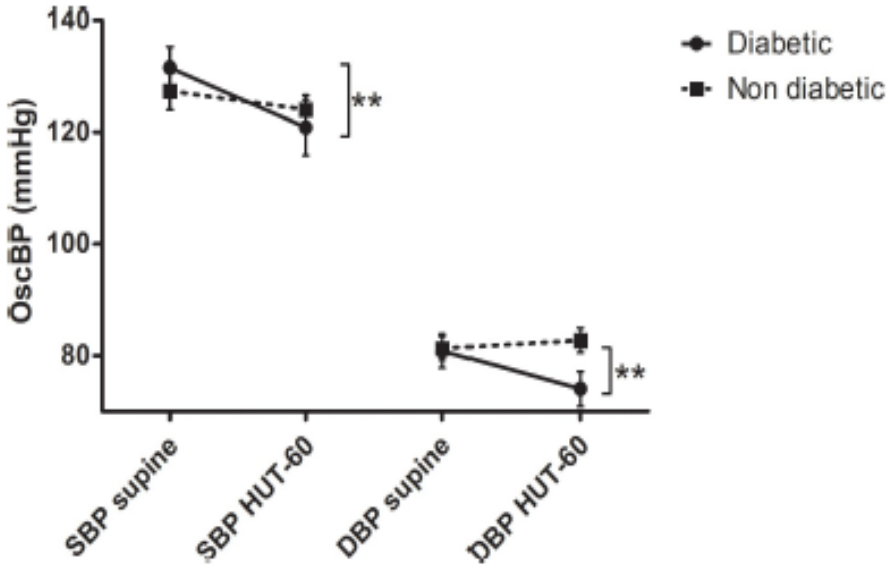

Fig 2. Changes in systolic (SBP) and diastolic (DBP) oscillometric blood pressure (OscBP) during transition from the supine position to HUT-60' (diabetic vs non diabetic). ** indicate the statistically significant drop in OscBP in diabetic patients (p< .01).

https://doi.org/10.1371/journal.pone.0208127.g002

Although a direct biologic mechanism may exist between baroreflex function and falls, given the relationship between impaired baroreflex function and orthostatic BP decrements [18], the study results do not seem to fully support the hypothesis that poor baroreflex function and orthostatic BP regulation are independent risk factors for falls in HD patients. While several baroreflex indices, as well as OscBP, were associated with falls in univariate logistic regression, adjusting the model for diabetic status resulted in no significant association between the baroreflex function/haemodynamic responses and falls.

The role of diabetes, in the context of our study, plays a crucial role as 34.9% of the patients classified as fallers had diabetic nephropathy as PRD, compared to only 12.9% in the group of non-fallers. Diabetic nephropathy represents an advanced stage of diabetes, which is commonly associated with cardiovascular autonomic neuropathy and chronic sympathetic overactivity, both of which can affect the baroreflex and potentially the haemodynamic responses to orthostasis [29]. Therefore, the higher proportion of diabetic patients amongst fallers is likely to be a main driver of the significant differences observed between fallers and non-fallers in terms of baroreflex function and BP response to orthostasis.

The point biserial correlation analysis performed in the subgroup of non-diabetic patients did not reveal any significant correlations between any of the baroreflex/haemodynamic variables and falls, which highlights the mediating effect of diabetes on the study results.

This is an interesting finding considering that diabetes has been found to be an independent risk factor for falls in HD patients [2], and our study results seem to indirectly suggest that impaired baroreflex and BP dysregulation may be one of the biological mechanisms underlying the higher occurrence of falls amongst diabetic HD patients.

Surprisingly, we did not find any differences in the SV, CO, TPR, HR, contSBP, and contDBP responses to the HUT-60' between fallers and non-fallers. This lack of effect may be

explained in light of the relatively short duration of the orthostatic challenge. Although 5 minutes of orthostasis are considered to be sufficient for the diagnosis of orthostatic hypotension, according to the current guidelines [20], it is possible that a longer orthostatic challenge could have yielded different results. For instance, Shaw et al., [10] examined the cardiovascular responses to orthostasis in a group of elderly residents in long-term facilities. They found that, during an orthostatic challenge, the decreases in contBP were larger in those with a history of falls, but only in the delayed phase of orthostasis (3–15 minutes) rather than at the initial phase (0–3 minutes). This might explain why we found a significant larger decrement in OscBP, but not in contBP between fallers and non-fallers: whilst OscBP assessment consists of single measurements, which capture the BP at a single time-frame, contBP may provide more useful information than single sphygmomanometer assessments, in terms of actual beat-to-beat variations of BP [30], but its measurement represents an average of several measurements over a given interval of interest. Therefore, the two type of BP measurements, despite being performed in the same phases, do not represent exactly the same haemodynamic data.

During HUT-60˚, for instance, the contSBP and contDBP reflect the overall BP performance over the 5 minutes of data acquisition and it is possible that a longer recording interval may also have revealed a larger decrement of BP in fallers. Moreover, the discrepancy between contBP and OscBP measurements during HUT-60˚ could also be explained in light of a possible hydrostatic effect: because postural changes can modify the distribution of hydrostatic pressures in fluid-filled body compartments [31], it is possible that the transition from supine to HUT-60˚ may have influenced to some extent the response of contBP due to the initial gravitational shift. On the other hand, during HUT-60˚, OscBP was measured when the patient was already in the upright position, and therefore this measurement would be less subjected to hydrostatic adjustments arising from the tilting procedure. Although we sought to minimise the hydrostatic effects of tilting by standardising the testing procedures, as described in S1 Protocol, it is possible that these may have played a role in the discrepancy observed between the two kinds of BP assessments.

It should also be acknowledged that the resting BP of the study participants was surprisingly low considering that HD patients are usually hypertensive. This relatively low BP may be explained in light of the strict testing standardisation procedures which were designed to ensure the best possible haemodynamic state balance (e.g. no caffeine, supine rest prior to the assessment, non-dialysis day), and also by a possible underestimation of BP from the Task Force Monitor [32]. Although this should not affect the study results, since the research aim was focused on exploring the relationship between the relative change in BP and falls, rather than the absolute values of BP, the generalisability of the study results to patients with higher or more poorly controlled resting BP should be cautious.

Only a few studies examined the BP changes in response to orthostasis in HD patients, and found no association between the BP response to a pre-dialysis [4] or post-dialysis [2, 33] orthostatic assessment and the patients' falling status. Nevertheless, these studies assessed the BP response by means of OscBP measurements after active standing, a procedure that may be subjected to standardisation issues compared to the head-up tilt test, which is considered the reference standard for the assessment of orthostatic hypotension [34].

In addition, it should be acknowledged that the tilting angle might also be partly responsible for the lack of response. Typically, angles of 60˚-90˚ are widely implemented in clinical practice [35] and thus tilting patients beyond 60˚ could have constituted a larger haemodynamic challenge and concomitant response.

The incidence of falls recorded was 1.11 falls/patient-year and is approximately 2.3 times greater than seen in the non-uraemic, community-dwelling elderly [36]. This confirms the increased risk of falling of HD patients compared with the general healthy population [2].

Although the current study was conducted in a small cohort of patients, our findings relating to the incidence of falls are broadly in agreement with those of larger observational studies. In particular, Desmet et al., [2], reported a yearly incidence of 1.18 falls/patient-year for their HD patients, which is very similar to that observed in our study (1.11 falls/patient-year). Additionally, the proportion of patients observed in our study, who experienced at least one fall during the 12-month follow-up (36.1%), is also very similar to that reported in previous research (28.3%) [6]. Therefore, our findings on falling behaviour in HD patients seem to be representative of this patient group, and results from this study may be generalised to the general population of CKD-5 patients undergoing HD therapy.

Limitations

First of all, the classification of patients in fallers and non-fallers was based on self-reported information. As previous research has highlighted how recalling information about falls might be subjected to misreporting [37], this could have resulted in some degree of misclassification in the group allocation. We sought to minimise this bias by following up prospectively the participants every month [38], although patients were also classified as fallers if they had experienced at least one fall in the previous 12 months: this kind of information is theoretically more susceptible to misreporting given the longer recall interval [39]. The decision to classify the patients with a previous history of falls also as fallers, regardless of the occurrence of any new fall event during the observational follow-up, was made to counterbalance another risk of bias, namely that of blindly assuming that all patients were free from the clinical outcome of interest, i.e. falls, at the beginning of the study.

In addition, the relatively small sample size did not allow the application of a more exhaustive, a priori, multivariate logistic regression analysis to more robustly test the interrelationships between baroreflex function, haemodynamic responses, and falls.

Conclusions

This study indicates that, at rest, HD patients classed as "fallers" present with worse baroreflex indexes reflecting how often the baroreflex is activated, as highlighted by the lower number of baroreceptor-mediated sequences of coupled HR and BP. Additionally, a significantly larger decrement of OscBP was observed in "fallers", even though other haemodynamic responses to HUT-60˚ were not seen to differ between fallers and non-fallers. Patients with falls were also more likely to have diabetes as PRD, and the diabetic status seems to at least partly mediate the relationship between baroreflex function/BP responses to orthostasis and falls. The short-term BP regulation warrants further investigation as BP drops during the transition from supine to an upright position may be implicated in the aetiology of falls in HD.

Supporting information

S1 File. Research dataset.
(XLSX)

S1 Protocol. Head-up tilt to 60 degrees (HUT-60˚) protocol.
(DOC)

S1 Table. Heart rate variability (HRV) data of study participants.
(DOCX)

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